FILE 'CAPLUS' ENTERED AT 17:44:01 ON 09 FEB 2002

FILE 'USPATFULL' ENTERED AT 17:44:01 ON 09 FEB 2002


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=> s IL(2a)6(5a)(inhibitor? or antagonist?)
L1         1053 IL(2A) 6(5A)(INHIBITOR? OR ANTAGONIST?)

=> s l1 and mucosit?
L2            9 L1 AND MUCOSIT?

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3            9 DUP REM L2 (0 DUPLICATES REMOVED)

=> d l3 abs ibib kwic 1-9

L3   ANSWER 1 OF 9  USPATFULL
AB     Novel aromatic heterocyclic compounds inhibit cytokines production
       involved in immunoregulation and inflammation such as interleukin-1 and
       tumor necrosis factor production. The compounds are therefore useful in
       pharmaceutic compositions for treating diseases or pathological
       conditions involving inflammation such as chronic inflammatory diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER:        2001:200183  USPATFULL
TITLE:                   Aromatic heterocyclic compounds and their use as
                         anti-inflammatory agents
INVENTOR(S):             Regan, John R., Larchmont, NY, United States
                         Hickey, Eugene R., Danbury, CT, United States
                         Moss, Neil, Ridgefield, CT, United States
                         Cywin, Charles L., Bethel, CT, United States
                         Pargellis, Christopher, West Redding, CT, United States
                         Gilmore, Thomas A., Middlebury, CT, United States

                              NUMBER         KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2001039290      A1   20011108
APPLICATION INFO.:       US 2001-808084     A1   20010314  (9)
RELATED APPLN. INFO.:    Division of Ser. No. US 1999-461446, filed on 14 Dec
                         1999, GRANTED, Pat. No. US 6228881 Division of Ser. No.
                         US 1998-181743, filed on 29 Oct 1998, GRANTED, Pat. No.
                         US 6080763

                                NUMBER         DATE
                         ------------------ --------
PRIORITY INFORMATION:    US 1997-64102      19971103 (60)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    BOEHRINGER INGELHEIM CORPORATION, 900 RIDGEBURY ROAD, P
                         O BOX 368, RIDGEFIELD, CT, 06877
NUMBER OF CLAIMS:        11
EXEMPLARY CLAIM:         1
LINE COUNT:              2147
```

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . cancer cachexia. The severity of key parameters of cachexia can be reduced by treatment with anti IL-6 antibodies or with **IL-6** receptor **antagonists** (Strassmann, et al., 1995, Cytokins Mol Ther. 1, 107). Several infectious diseases, such as influenza, indicate IL-6 and IFN alpha. . .
SUMM . . . been attempted in a number of disease states including burn-wound healing, skin-graft resolutiona as well as cytostatic and radiotherapy induced **mucositis** (Masucci, 1996, Medical Oncology 13: 149). GM-CSF also appears to play a role in the replication of human immunodeficiency virus. . .

L3 ANSWER 2 OF 9 USPATFULL
AB A method of reducing or inhibiting **mucositis** in a patient, which includes administering an inflammatory cytokine inhibitor or a mast cell inhibitor, or a combination thereof, is disclosed

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2001:123589 USPATFULL
TITLE:	Methods and compositions for treating and preventing **mucositis**
INVENTOR(S):	Sonis, Stephen T., Wayland, MA, United States Fey, Edward G., Boston, MA, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001011097	A1	20010802
APPLICATION INFO.:	US 2001-800855	A1	20010307 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1999-265299, filed on 9 Mar 1999, PENDING Continuation-in-part of Ser. No. US 1998-65012, filed on 23 Apr 1998, ABANDONED		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-77977	19980313 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	ARNALL GOLDEN & GREGORY, LLP, 2800 ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, ATLANTA, GA, 30309-3450
NUMBER OF CLAIMS:	34
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	1 Drawing Page(s)
LINE COUNT:	526

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Methods and compositions for treating and preventing **mucositis**
AB A method of reducing or inhibiting **mucositis** in a patient, which includes administering an inflammatory cytokine inhibitor or a mast cell inhibitor, or a combination thereof, is. . .
SUMM [0002] This invention relates to methods and compositions for treating and preventing **mucositis**.
SUMM [0003] **Mucositis** is the destruction of the oral mucosal epithelium, which results in erythema, ulcerations and severe pain in the oral cavity. **Mucositis** often arises as a complication of antineoplastic therapy, such as cancer chemotherapy and/or radiation therapy. The painful ulcerative lesions of **mucositis** can cause patients to restrict their oral intake; as a result, they lose weight and suffer from fever associated with dehydration. Severe **mucositis** can necessitate the de-escalation of a planned

chemo/radio-therapeutic dosing regimen to prevent further damage to the oral mucosa.

SUMM [0004] An even more serious consequence of **mucositis** is that the lesions can act as sites of secondary infections and as portals of entry for endogenous oral microorganisms. **Mucositis** is therefore a significant risk factor for life-threatening systemic infection (septicemia); the risk of systemic infection is exacerbated by concomitant neutropenia, which is another complication associated with chemotherapy. Patients with **mucositis** and neutropenia have a relative risk of septicemia that is at least four times greater than that of individuals without **mucositis**.

SUMM [0005] The overall frequency of **mucositis** varies; it is influenced by the patient's diagnosis, age, and level of oral health, as well as the type, dose,. . . and frequency of drug or radiation administration. Approximately 40% of all patients who receive cancer chemotherapy suffer some degree of **mucositis**, and virtually 100% of patients treated with radiation therapy for head and neck tumors develop **mucositis**. The frequency of severe **mucositis** in patients undergoing high risk protocols is over 60%. About 50% of individuals develop lesions severe enough to require modification. . .

SUMM [0006] The development of effective methods for treating and preventing **mucositis** has been hampered by a lack of understanding of the pathophysiology of this condition, and by the inconsistency in patient. . .

SUMM [0007] The invention features methods for treating and preventing **mucositis**. The invention is based, in part, on the recognition that **mucositis** is a complex biological process resulting from the cumulative and interactive effects of radiation and/or chemotherapy with epithelial connective tissue. . .

SUMM [0008] We hypothesize that **mucositis** represents a clinical outcome due to a complex interaction of local tissue (connective tissue, endothelium, epithelium) toxicity, the level of. . .

SUMM . . . inflammatory cells expressing pro-inflammatory cytokines occurs during the breakdown of the mucosa and peaks just prior to the acme of **mucositis**. Bacterial colonization of the damaged epithelium occurs and is accelerated by the patient's myelosuppressed state. Typically the nadir follows a day or so after peak **mucositis**. Bacterial cell wall products from both gram positive and gram negative organisms likely then penetrate the injured mucosa and further. . .

SUMM [0010] According to the invention, **mucositis** can be treated, or even prevented, by the administration of inflammatory cytokine inhibitors, MMP inhibitors, and/or mast cell inhibitors. The. . . these inhibitors with an anti-inflammatory agent and/or an antimicrobial agent provides an even more effective regime for preventing and treating **mucositis**.

SUMM [0011] The invention features a method of reducing or inhibiting **mucositis**, in a patient suffering from **mucositis** or at risk for **mucositis**; the method includes administering to the patient a first therapeutic agent in an amount sufficient to inhibit **mucositis**, where the first therapeutic agent is an inflammatory cytokine inhibitor, a mast cell inhibitor, an MMP inhibitor, or a combination. . . A preferred MMP inhibitor is a tetracycline such as minocycline, which used by itself in low doses is an effective **mucositis** agent that does not primarily act as an antibiotic. Other members of the tetracycline family can be used as well, e.g., chlortetracycline and oxytetracycline. An example of a **mucositis** that can be reduced or inhibited according to the invention is oral **mucositis**.

SUMM [0012] The invention also features a method of treating, inhibiting, or preventing **mucositis** in the human patient by administering to the patient first and second different therapeutic agents, the first agent being an. . . inhibitor; examples of COX-1 inhibitors are indomethacin and flurbriprofin. In other preferred embodiments, the first agent is an inflammatory cytokine **inhibitor** selected from an **IL-6 inhibitor**, a TNF-alpha **inhibitor**, an IL-1 inhibitor, and an interferon-gamma inhibitor. A preferred combination is a TNF-alpha inhibitor combined with an MMP inhibitor such. . .

SUMM [0014] In another preferred method, the first therapeutic agent, in an amount sufficient to inhibit **mucositis**, and the third therapeutic agent, in an amount sufficient to inhibit infection, are administered. Preferably, the first therapeutic agent and. . .

SUMM [0015] The **mucositis** being treated can be induced by antineoplastic therapy; for example, it can be induced by chemotherapy or by radiation therapy.. . .

SUMM [0016] The invention further features a pharmaceutical composition for treating oral **mucositis** that includes (a) a first therapeutic agent including an inflammatory cytokine inhibitor, a mast cell inhibitor, an MMP inhibitor or. . . agent; and (c) a pharmaceutically acceptable carrier. The first and second therapeutic agents are present in amounts sufficient to inhibit **mucositis** in a patient suffering from **mucositis** or at risk for **mucositis**. Preferably, the composition is formulated into a lozenge, a tablet, an oral rinse, an oral paste, or an oral gel.. . .

DRWD [0017] FIG. 1 is a schematic representation illustrating the four phases of **mucositis** development and resolution.

DETD [0018] The invention features methods and compositions for reducing and inhibiting **mucositis** that include administering inflammatory cytokine inhibitors and/or mast cell inhibitors.

DETD [0019] The invention is based, in part, on the development of a new mechanistic scheme for the physiological basis of **mucositis**. According to this scheme, the development and resolution of **mucositis** occurs in four interrelated phases: (i) an inflammatory/vascular response; (ii) a degenerative connective tissue and/or epithelial phase; (iii) an ulcerative/bacteriological. . .

DETD . . . in the local levels of cytotoxic agents. Both IL-1 and TNF-.alpha. cause local tissue damage, and thereby initiate and accelerate **mucositis**.

DETD . . . also based, in part, on the discovery that proliferation of mast cells plays a key role in the development of **mucositis**. Mast cells are granule-containing secretory cells which are present in mucosal and connective tissues, and which can migrate within these. . .

DETD . . . the mast cells or the action of the mediators released by mast cells can be used to treat and prevent **mucositis**. Mast cell inhibitors are chemical or biological agents that suppress or inhibit the function of mast cells, or the mediators. . .

DETD [0034] According to the invention, inflammatory cytokine inhibitors can also be used to treat and prevent **mucositis**. Inflammatory cytokine inhibitors are chemical or biological agents that suppress or inhibit inflammatory cytokines. Such inhibitors include pyridinyl imidazoles, bicyclic. . .

DETD [0035] Anti-inflammatory agents can be used in combination with inflammatory cytokine and/or mast cell inhibitors to treat and prevent **mucositis** according to the invention. Examples of anti-inflammatory agents that can be used in the present invention

include the non-steroidal anti-inflammatory. . .

DETD . . . for the elevated production of prostaglandins during inflammation. COX-2 inhibitors are especially useful where the invention is used to treat **mucositis** in cancer patients undergoing chemotherapy or radiation therapy, because of the gastrointestinal tolerability of these inhibitors. COX-2 inhibitors that can. . .

DETD . . . agents in combination with the agents described above can result in an even more effective method for treating and preventing **mucositis**. Examples of antimicrobial agents that can be used include agents with spectrum for gram positive and gram negative organisms. Specific. . .

DETD [0041] Other agents that can be used to treat or prevent **mucositis** include the nuclear transcription factor kappa-B (NF-.kappa.B) activation inhibitors capsaicin and resiniferatoxin.

DETD [0044] Since the compositions of the invention can help prevent **mucositis**, administration of the compositions should preferably precede the initial dose of antineoplastic therapy by at least 24 hours. Daily treatment. . .

DETD [0059] For treatment according to the methods described herein, patients are dosed with a topical application of **mucositis** medication as a troche or lozenge, beginning the evening before the first dose of chemotherapy. The lozenge contains therapeutic doses. . .

DETD . . . assure exposure of the drug to the oropharynx. The fourteen-day dosing period provides coverage through the first three phases of **mucositis** development.

DETD . . . dose of radiation of about 60 Gy, given in divided doses over a 6-week to 8-week period. Early signs of **mucositis** are noted at doses of around 10 Gy, and frank breakdown of the mucosa is seen at around 25 Gy.

DETD [0063] Beginning with the second week of this type of radiation therapy, patients receive **mucositis** medication 2 hours prior to each daily dose of radiation, which is typically given 5 days per week. Subsequent **mucositis** medication is given 2 hours, 6 hours, and 12 hours following daily radiation. Since myelosuppression is not an issue for patients being radiated for head and neck cancers, the **mucositis** preparation includes mast cell inhibitors, cytokine inhibitors, and anti-inflammatory agents, but no anti-microbial agents. Patients do not receive **mucositis** medication on days on which they are not radiated. The protocol is followed until radiation dosing is completed.

DETD . . . specific anti-cancer drugs for treatment of this form of tumor, this group of patients is at particular risk for developing **mucositis**. Patients in this group begin dosing with **mucositis** medication two hours prior to chemotherapy administration. They continue taking **mucositis** medication every 4 hours, while awake, for at least the next 48 hours. The regimen is repeated for each dosing. . .

DETD . . . to treat and prevent conditions such as lichen planus and graft-vs-host disease, which have similar biological mechanisms to that of **mucositis**.

CLM What is claimed is:

1. A method of treating, inhibiting, or preventing **mucositis** in a human patient, said method comprising administering to said patient first and second different therapeutic agents, wherein said first. . .

4. The method of claim 1, wherein the first agent is an inflammatory cytokine **inhibitor** selected from an **IL-6 inhibitor**, a TNF-alpha **inhibitor**, an IL-1 inhibitor, and an interferon-gamma inhibitor.

15. A method of treating, inhibiting, or preventing **mucositis** in a human patient, said method comprising administering to said patient an effective amount of a therapeutic agent selected from. . .
22. The method of claim 1, wherein said **mucositis** is induced by antineoplastic therapy.

23. The method of claim 22, wherein said **mucositis** is induced by chemotherapy.

24. The method of claim 22, wherein said **mucositis** is induced by radiation therapy.

27. The method of claim 1, wherein said **mucositis** is oral **mucositis**.

28. A pharmaceutical composition for treating oral **mucositis** comprising (a) a first therapeutic agent comprising an NSAID, an inflammatory cytokine inhibitor, or a mast cell inhibitor; (b) a. . . and (c) a pharmaceutically acceptable carrier, wherein said first and second therapeutic agents are present in amounts sufficient to inhibit **mucositis** in a patient suffering from **mucositis** or at risk for **mucositis**.

L3 ANSWER 3 OF 9 USPATFULL

AB Disclosed are novel aromatic heterocyclic compounds of the formula(I) wherein Ar.sub.1,Ar.sub.2,L,Q and X are described herein. The compounds are useful in pharmaceutic compositions for treating diseases or pathological conditions involving inflammation such as chronic inflammatory diseases. Also disclosed are processes of making such compounds. ##STR1##

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2001:235250 USPATFULL
TITLE: Method of treating cytokine mediated diseases or conditions
INVENTOR(S): Cirillo, Pier F., Woodbury, CT, United States
Gilmore, Thomas A., Middlebury, CT, United States
Hickey, Eugene R., Danbury, CT, United States
Regan, John R., Larchmont, NY, United States
Zhang, Lin-Hua, New Fairfield, CT, United States
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6333325	B1	20011225
APPLICATION INFO.:	US 2001-871559		20010531 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-484638, filed on 18 Jan 2000

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-116400	19990119 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Ramsuer, Robert W.

LEGAL REPRESENTATIVE: Raymond, Robert P., Bottino, Anthony P., Stempel, Alan R.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
LINE COUNT: 2234
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . cancer cachexia. The severity of key parameters of cachexia can be reduced by treatment with anti IL-6 antibodies or with **IL-6** receptor **antagonists** (Strassmann, et al., 1995, Cytokins Mol Ther. 1, 107). Several infectious diseases, such as influenza, indicate IL-6 and IFN alpha. . .
SUMM . . . been attempted in a number of disease states including burn-wound healing, skin-graft resolution as well as cytostatic and radiotherapy induced **mucositis** (Masucci, 1996, Medical Oncology 13: 149). GM-CSF also appears to play a role in the replication of human immunodeficiency virus. . .

L3 ANSWER 4 OF 9 USPATFULL
AB Disclosed are novel aromatic heterocyclic compounds of the formula(I) wherein Ar.sub.1,Ar.sub.2,L,Q and X are described herein. The compounds are useful in pharmaceutic compositions for treating diseases or pathological conditions involving inflammation such as chronic inflammatory diseases. Also disclosed are processes of making such compounds. ##STR1##

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2001:226669 USPATFULL
TITLE: Aromatic heterocyclic compounds as antiinflammatory agents
INVENTOR(S): Cirillo, Pier F., Woodbury, CT, United States
Regan, John R., Larchmont, NY, United States
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6329415	B1	20011211
APPLICATION INFO.:	US 2001-891579		20010626 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 2000-484638, filed on 18 Jan 2000

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-116400	19990101 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Ramsuer, Robert W.
LEGAL REPRESENTATIVE: Raymond, Robert P., Bottino, Anthony P., Stempel, Alan R.
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 2204
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . cancer cachexia. The severity of key parameters of cachexia can be reduced by treatment with anti IL-6 antibodies or with **IL-6** receptor **antagonists** (Strassmann, et al., 1995, Cytokins Mol Ther. 1, 107). Several infectious diseases, such as influenza, indicate IL-6 and IFN alpha. . .

SUMM . . . been attempted in a number of disease states including burn-wound healing, skin-graft resolution as well as cytostatic and radiotherapy induced **mucositis** (Masucci, 1996, Medical Oncology 13: 149). GM-CSF also appears to play a role in the replication of human immunodeficiency virus. . .

L3 ANSWER 5 OF 9 USPATFULL

AB Disclosed are novel aromatic heterocyclic compounds of the formula (I) wherein Ar.sub.1, Ar.sub.2, L, Q and X are described herein. The compounds are useful in pharmaceutic compositions for treating diseases or pathological conditions involving inflammation such as chronic inflammatory diseases. Also disclosed are processes of making such compounds. ##STR1##

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2001:208887 USPATFULL
TITLE:	Aromatic heterocyclic compound as antiinflammatory agents
INVENTOR(S):	Cirillo, Pier F., Woodbury, CT, United States Gilmore, Thomas A., Middlebury, CT, United States Hickey, Eugene R., Danbury, CT, United States Regan, John R., Larchmont, NY, United States Zhang, Lin-Hua, New Fairfield, CT, United States
PATENT ASSIGNEE(S):	Boerhinger Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6319921	B1	20011120
APPLICATION INFO.:	US 2000-484638		20000118 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-116400	19990119 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Ramsuer, Robert W.
LEGAL REPRESENTATIVE:	Raymond, Robert P., Bottino, Anthony P., Stempel, Alan R.
NUMBER OF CLAIMS:	19
EXEMPLARY CLAIM:	1
LINE COUNT:	2297

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . cancer cachexia. The severity of key parameters of cachexia can be reduced by treatment with anti IL-6 antibodies or with **IL-6** receptor **antagonists** (Strassmann, et al., 1995, Cytokins Mol Ther. 1, 107). Several infectious diseases, such as influenza, indicate IL-6 and IFN alpha. . .

SUMM . . . been attempted in a number of disease states including burn-wound healing, skin-graft resolution as well as cytostatic and radiotherapy induced **mucositis** (Masucci, 1996, Medical Oncology 13: 149). GM-CSF also appears to play a role in the replication of human immunodeficiency virus. . .

L3 ANSWER 6 OF 9 USPATFULL

AB Disclosed are novel aromatic heterocyclic compounds of the formula(I) wherein Ar.sub.1,Ar.sub.2,L,Q and X are described herein. The compounds are useful in pharmaceutic compositions for treating diseases or

pathological conditions. Also disclosed are processes of making such compounds. ##STR1##

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2001:168261 USPATFULL
TITLE:	Aromatic heterocyclic compounds as anti-inflammatory agents
INVENTOR(S):	Cirillo, Pier F., Woodbury, CT, United States Hickey, Eugene R., Danbury, CT, United States Regan, John R., Larchmont, NY, United States
PATENT ASSIGNEE(S):	Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6297381	B1	20011002
APPLICATION INFO.:	US 2000-503385		20000214 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-124147	19990312 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Shah, Mukund J.
ASSISTANT EXAMINER:	Patel, Sudhaker B.
LEGAL REPRESENTATIVE:	Raymond, Robert P., Bottino, Anthony P., Stempel, Alan R.
NUMBER OF CLAIMS:	20
EXEMPLARY CLAIM:	1
LINE COUNT:	1389

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . cancer cachexia. The severity of key parameters of cachexia can be reduced by treatment with anti IL-6 antibodies or with **IL-6** receptor **antagonists** (Strassmann, et al., 1995, Cytokins Mol Ther. 1, 107). Several infectious diseases, such as influenza, indicate IL-6 and IFN alpha. . .

SUMM . . . been attempted in a number of disease states including burn-wound healing, skin-graft resolution as well as cytostatic and radiotherapy induced **mucositis** (Masucci, 1996, Medical Oncology 13: 149). GM-CSF also appears to play a role in the replication of human immunodeficiency virus. . .

L3 ANSWER 7 OF 9 USPATFULL

AB Disclosed are novel aromatic polycyclo heterocyclic compounds of the formula(I) wherein A, B, C, G, Ar, L, Q and X are described herein. The compounds are useful in pharmaceutical compositions for treating diseases or pathological conditions involving inflammation such as chronic inflammatory disease. Also disclosed are processes of making such compounds. ##STR1##

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2001:82778 USPATFULL
TITLE:	Polycyclo heterocyclic derivatives as antiinflammatory agents
INVENTOR(S):	Cirillo, Pier F., Woodbury, CT, United States Hickey, Eugene R., Danbury, CT, United States Regan, John R., Larchmont, NY, United States Zhang, Lin-Hua, New Fairfield, CT, United States

PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6242453	B1	20010605
APPLICATION INFO.:	US 2000-503263		20000214 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-121178	19990222 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Raymond, Richard L.
ASSISTANT EXAMINER: Rao, Deepak R.
LEGAL REPRESENTATIVE: Raymond, Robert P., Bottino, Anthony P., Stempel, Alan R.
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
LINE COUNT: 1136
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . us cachexia. The severity of key parameters of cachexia can be reduced by treatment with anti IL-6 antibodies or with **IL-6** receptor **antagonists** (Strassmann, et al., 1995, Cytokins Mol Ther. 1, 107). Several infectious diseases, such as influenza, indicate IL-6 and IFN alpha. . .
SUMM . . . been attempted in a number of disease states including burn-wound healing, skin-graft resolution as well as cytostatic and radiotherapy induced **mucositis** (Masucci, 1996, Medical Oncology 13: 149). GM-CSF also appears to play a role in the replication of human immunodeficiency virus. . .

L3 ANSWER 8 OF 9 USPATFULL
AB Novel aromatic heterocyclic compounds inhibit cytokines production involved in immunoregulation and inflammation such as interleukin-1 and tumor necrosis factor production. The compounds are therefore useful in pharmaceutic compositions for treating diseases or pathological conditions involving inflammation such as chronic inflammatory diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2001:67692 USPATFULL
TITLE: Aromatic heterocyclic compounds and their use as anti-inflammatory agents
INVENTOR(S): Regan, John R., Larchmont, NY, United States
Cirillo, Pier F., Woodbury, CT, United States
Hickey, Eugene R., Danbury, CT, United States
Moss, Neil, Ridgefield, CT, United States
Cywin, Charles L., Bethel, CT, United States
Pargellis, Christopher, West Redding, CT, United States
Gilmore, Thomas A., Middlebury, CT, United States
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6228881	B1	20010508
APPLICATION INFO.:	US 1999-461446		19991214 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-181743, filed on 29 Oct

1998

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-64102	19971103 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Owens, Amelia
LEGAL REPRESENTATIVE: Raymond, Robert P., Bottino, Anthony P., Stempel, Alan R.
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
LINE COUNT: 2086
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . cancer cachexia. The severity of key parameters of cachexia can be reduced by treatment with anti IL-6 antibodies or with **IL-6** receptor **antagonists** (Strassmann, et al, 1995, Cytokins Mol Ther. 1, 107). Several infectious diseases, such as influenza, indicate IL-6 and IFN alpha. . . been attempted in a number of disease states including bum-wound healing, skin-graft resolutions as well as cytostatic and radiotherapy induced **mucositis** (Masucci, 1996, Medical Oncology 13: 149). GM-CSF also appears to play a role in the replication of human immunodeficiency virus. . .

L3 ANSWER 9 OF 9 USPATFULL
AB Novel aromatic heterocyclic compounds inhibit cytokines production involved in immunoregulation and inflammation such as interleukin-1 and tumor necrosis factor production. The compounds are therefore useful in pharmaceutic compositions for treating diseases or pathological conditions involving inflammation such as chronic inflammatory diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2000:80771 USPATFULL
TITLE: Aromatic heterocyclic compounds and their use as anti-inflammatory agents
INVENTOR(S): Regan, John R., Larchmont, NY, United States
Cirillo, Pier F., Woodbury, CT, United States
Hickey, Eugene R., Danbury, CT, United States
Moss, Neil, Ridgefield, CT, United States
Cywin, Charles L., Bethel, CT, United States
Pargellis, Christopher, West Redding, CT, United States
Gilmore, Thomas A., Middlebury, CT, United States
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6080763		20000627
APPLICATION INFO.:	US 1998-181743		19981029 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-64102	19971103 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Owens, Amelia
LEGAL REPRESENTATIVE: Raymond, Robert P., Bottino, Anthony P., Stempel, Alan

R.
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
LINE COUNT: 2027
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . cancer cachexia. The severity of key parameters of cachexia can be reduced by treatment with anti IL-6 antibodies or with **IL-6** receptor **antagonists** (Strassmann, et al., 1995, Cytokins Mol Ther. 1, 107). Several infectious diseases, such as influenza, indicate IL-6 and IFN alpha. . .
SUMM . . . been attempted in a number of disease states including burn-wound healing, skin-graft resolutiona as well as cytostatic and radiotherapy induced **mucositis** (Masucci, 1996, Medical Oncology 13: 149). GM-CSF also appears to play a role in the replication of human immunodeficiency virus. . .

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     (FILE 'HOME' ENTERED AT 17:43:44 ON 09 FEB 2002)

     FILE 'CAPLUS, USPATFULL' ENTERED AT 17:44:01 ON 09 FEB 2002
L1          1053 S IL(2A)6(5A)(INHIBITOR? OR ANTAGONIST?)
L2             9 S L1 AND MUCOSIT?
L3             9 DUP REM L2 (0 DUPLICATES REMOVED)
L4          1672 S THALIDOMIDE
L5            22 S L4 AND MUCOSIT?
L6             3 S THALIDOMIDE(P) MUCOSIT?
L7            22 DUP REM L5 (0 DUPLICATES REMOVED)
L8          7309 S (IL(2A)1(5A)(INHIBIT? OR ANTAGONIST?) OR INTERFERON(2A)GAMMA(
L9            60 S L8 AND MUCOSITI?
L10           60 DUP REM L9 (0 DUPLICATES REMOVED)
L11           36 S L10 AND PY<=1998

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=> s thalidomide
L4        1672 THALIDOMIDE

=> s l4 and mucosit?
L5          22 L4 AND MUCOSIT?

=> s thalidomide(p) mucosit?
L6           3 THALIDOMIDE(P) MUCOSIT?

=> d l6 abs ibib kwic 1-3
```

L6 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS

AB This review summarises the large no. of locally and systemically applied preventive and therapeutic interventions of **mucositis** in patients with cancer. The need for further elucidation of the pathophysiol. and for optimization of trial methodol. is emphasized. Data from trials in animal models and preliminary data in patients indicate that cytokines such as interleukin-1, interleukin-11, TGF-.beta.3 and keratinocyte growth factor could reduce the incidence of **mucositis**. Other potentially useful agents are the angiogenesis-inhibiting drug **thalidomide**, the cytoprotector amifostine and the pineal hormone melatonin.

ACCESSION NUMBER: 2000:816317 CAPLUS
TITLE: Prevention and management of mucositis in patients with cancer
AUTHOR(S): Herrstedt, Jorn
CORPORATE SOURCE: Department of Oncology, Copenhagen University Hospital, Herlev, DK-2730, Den.
SOURCE: Int. J. Antimicrob. Agents (2000), 16(2), 161-163
CODEN: IAAGEA; ISSN: 0924-8579
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB This review summarises the large no. of locally and systemically applied preventive and therapeutic interventions of **mucositis** in patients with cancer. The need for further elucidation of the pathophysiol. and for optimization of trial methodol. is emphasized. Data from trials in animal models and preliminary data in patients indicate that cytokines such as interleukin-1, interleukin-11, TGF-.beta.3 and keratinocyte growth factor could reduce the incidence of **mucositis**. Other potentially useful agents are the angiogenesis-inhibiting drug **thalidomide**, the cytoprotector amifostine and the pineal hormone melatonin.

L6 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS

AB A method of reducing or inhibiting mucositis in a patient includes administering an inflammatory cytokine inhibitor or a mast cell inhibitor, or a combination thereof.

ACCESSION NUMBER: 1999:594911 CAPLUS
DOCUMENT NUMBER: 131:209126
TITLE: Methods and compositions using inflammatory cytokine inhibitors and mast cell inhibitors for treating and preventing mucositis
INVENTOR(S): Sonis, Stephen T.; Fey, Edward G.
PATENT ASSIGNEE(S): Mucosal Therapeutics Llc, USA

SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9945910	A2	19990916	WO 1999-US5437	19990312
WO 9945910	A3	20000210		
W: AU, BR, CA, IL, JP, MX, NZ, PL				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9930837	A1	19990927	AU 1999-30837	19990312
BR 9908857	A	20001031	BR 1999-8857	19990312
EP 1064001	A2	20010103	EP 1999-912467	19990312
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 2001011097	A1	20010802	US 2001-800855	20010307

PRIORITY APPLN. INFO.:
US 1998-77977 P 19980313
US 1998-65012 A 19980423
US 1999-265299 A 19990309
WO 1999-US5437 W 19990312

IT 50-35-1, **Thalidomide** 53-86-1, Indomethacin 79-17-4, Aminoguanidine 113-00-8, Guanidine 5104-49-4, Flurbiprofen 10118-90-8, Minocycline
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

L6 ANSWER 3 OF 3 USPATFULL
AB A method of reducing or inhibiting mucositis in a patient, which includes administering an inflammatory cytokine inhibitor or a mast cell inhibitor, or a combination thereof, is disclosed

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2001:123589 USPATFULL
TITLE: Methods and compositions for treating and preventing mucositis
INVENTOR(S): Sonis, Stephen T., Wayland, MA, United States
Fey, Edward G., Boston, MA, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001011097	A1	20010802
APPLICATION INFO.:	US 2001-800855	A1	20010307 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-265299, filed on 9 Mar 1999, PENDING Continuation-in-part of Ser. No. US 1998-65012, filed on 23 Apr 1998, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-77977	19980313 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ARNALL GOLDEN & GREGORY, LLP, 2800 ONE ATLANTIC CENTER,

1201 WEST PEACHTREE STREET, ATLANTA, GA, 30309-3450
NUMBER OF CLAIMS: 34
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 526
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0012] The invention also features a method of treating, inhibiting, or preventing **mucositis** in the human patient by administering to the patient first and second different therapeutic agents, the first agent being an. . . as a tetracycline, eg, minocycline. Exemplary NO inhibitors are aminoguanidine and guanidine. Another TNF-alpha inhibitor that can be used is **thalidomide**. Mast cell inhibitors can be antihistamines, serine protease inhibitors, or degranulation inhibitors.
DETD [0034] According to the invention, inflammatory cytokine inhibitors can also be used to treat and prevent **mucositis**. Inflammatory cytokine inhibitors are chemical or biological agents that suppress or inhibit inflammatory cytokines. Such inhibitors include pyridinyl imidazoles, bicyclic imidazoles, oxpentifylline, **thalidomide** and gabexate mesilate.

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(FILE 'HOME' ENTERED AT 17:43:44 ON 09 FEB 2002)

FILE 'CAPLUS, USPATFULL' ENTERED AT 17:44:01 ON 09 FEB 2002
L1 1053 S IL(2A)6(5A)(INHIBITOR? OR ANTAGONIST?)
L2 9 S L1 AND MUCOSIT?
L3 9 DUP REM L2 (0 DUPLICATES REMOVED)
L4 1672 S THALIDOMIDE
L5 22 S L4 AND MUCOSIT?
L6 3 S THALIDOMIDE(P) MUCOSIT?

=> dup rem l5
PROCESSING COMPLETED FOR L5
L7 22 DUP REM L5 (0 DUPLICATES REMOVED)

=> d l7 abs ibib kwic 1-22

L7 ANSWER 1 OF 22 USPATFULL
AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

ACCESSION NUMBER: 2002:22131 USPATFULL
TITLE: 18 Human secreted proteins
INVENTOR(S): Shi, Yanggu, Gaithersburg, MD, UNITED STATES
Young, Paul E., Gaithersburg, MD, UNITED STATES
Ebner, Reinhard, Gaithersburg, MD, UNITED STATES
Soppet, Daniel R., Centreville, VA, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES

NUMBER	KIND	DATE

PATENT INFORMATION: US 2002012966 A1 20020131
APPLICATION INFO.: US 2001-768826 A1 20010125 (9)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2000-US22350, filed on 15 Aug 2000, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-148759	19990816 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 18157

SUMM . . . 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); **Thalidomide**; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

SUMM . . . intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of **mucositis** (mouth ulcers) that result from chemotherapy and viral infections.

DETD . . . that may be administered in combination with the Therapeutics of the invention include, but are not limited to, prednisolone, methotrexate, **thalidomide**, methoxsalen, rapamycin, leflunomide, mizoribine (BREDIINNTM), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKTV.RTM.3 (muromonab-CD3), SANDIMMUNE.TM., NEORAL.TM., SANGDYA.TM. (cyclosporine), PROGRAF.RTM. (FK506,. . .

DETD [1109] Additional anti-angiogenic factors that may also be utilized within the context of the present invention include **Thalidomide** , (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman J Pediatr. Surg. 28:445-51 (1993)); an integrin alpha v. . .

L7 ANSWER 2 OF 22 USPATFULL

AB The present invention relates to novel human uteroglobin-like polypeptides and isolated nucleic acids containing the coding regions of the genes encoding such polypeptides. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human uteroglobin-like polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human uteroglobin-like polypeptides.

ACCESSION NUMBER: 2002:12261 USPATFULL
TITLE: Uteroglobin-like polynucleotides, polypeptides, and antibodies
INVENTOR(S): Ni, Jian, Germantown, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002006640	A1	20020117
APPLICATION INFO.:	US 2001-846258	A1	20010502 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2000-US30326, filed on 3 Nov 2000, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-163395	19991104 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
LINE COUNT: 12076

SUMM . . . 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); **Thalidomide**; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

SUMM . . . intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of **mucositis** (mouth ulcers) that result from chemotherapy and viral infections.

DETD . . . that may be administered in combination with the Therapeutics of the invention include, but are not limited to, prednisolone, methotrexate, **thalidomide**, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ.TM.), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT.RTM. 3 (muromonab-CD3), SANDIMMUNE.TM., NEORAL.TM., SANGDYA.TM. (cyclosporine), PROGRAF.RTM.. . .

DETD [0934] Additional anti-angiogenic factors that may also be utilized within the context of the present invention include **Thalidomide**, (Celgene, Warren, N.J.); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman J Pediatr. Surg. 28:445-51 (1993)); an integrin alpha v. . .

L7 ANSWER 3 OF 22 USPATFULL

AB The present invention relates to novel human RIP polypeptides and isolated nucleic acids containing the coding regions of the genes encoding such polypeptides. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human RIP polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human RIP polypeptides.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:8489 USPATFULL
TITLE: Retinoid receptor interacting polynucleotides, polypeptides, and antibodies
INVENTOR(S): Shi, Yanggu, Gaithersburg, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002004489	A1	20020110
APPLICATION INFO.:	US 2001-788600	A1	20010221 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2000-US22351, filed on 15 Aug 2000, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-148757	19990816 (60)
	US 2000-189026	20000314 (60)

09/800,855

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
LINE COUNT: 11257
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); **Thalidomide**; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.
SUMM . . . intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of **mucositis** (mouth ulcers) that result from chemotherapy and viral infections.
DETD . . . that may be administered in combination with the Therapeutics of the invention include, but are not limited to, prednisolone, methotrexate, **thalidomide**, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ.TM.), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT.RTM. 3 (muromonab-CD3), SANDIMMUNE.TM., NEORAL.TM., SANGDYA.TM. (cyclosporine), PROGRAF.RTM.. . .
DETD [0880] Additional anti-angiogenic factors that may also be utilized within the context of the present invention include **Thalidomide** , (Celgene, Warren, N.J.); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman J Pediatr. Surg. 28:445-51 (1993)); an integrin alpha v. . .

L7 ANSWER 4 OF 22 USPATFULL
AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2001:155766 USPATFULL
TITLE: 49 human secreted proteins
INVENTOR(S): Moore, Paul A., Germantown, MD, United States
Ruben, Steven M., Oley, MD, United States
Olsen, Henrik S., Gaithersburg, MD, United States
Shi, Yanggu, Gaithersburg, MD, United States
Rosen, Craig A., Laytonsville, MD, United States
Florence, Kimberly A., Rockville, MD, United States
Soppet, Daniel R., Centreville, VA, United States
Lafleur, David W., Washington, DC, United States
Endress, Gregory A., Potomac, MD, United States
Ebner, Reinhard, Gaithersburg, MD, United States
Komatsoulis, George, Silver Spring, MD, United States
Duan, Roxanne D., Bethesda, MD, United States

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2001021700	A1	20010913	
APPLICATION INFO.:	US 2000-739254	A1	20001219	(9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-511554, filed on 23 Feb 2000, ABANDONED Continuation-in-part of Ser. No. WO 1999-US19330, filed on 24 Aug 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-97917	19980825 (60)
	US 1998-98634	19980831 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 15462
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); **Thalidomide**; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.
SUMM . . . the small intestine mucosa. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, may also stimulate healing of **mucositis** (mouth ulcers) that result from chemotherapy and viral infections.

L7 ANSWER 5 OF 22 USPATFULL
AB A method of reducing or inhibiting **mucositis** in a patient, which includes administering an inflammatory cytokine inhibitor or a mast cell inhibitor, or a combination thereof, is disclosed

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2001:123589 USPATFULL
TITLE: Methods and compositions for treating and preventing **mucositis**
INVENTOR(S): Sonis, Stephen T., Wayland, MA, United States
Fey, Edward G., Boston, MA, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001011097	A1	20010802
APPLICATION INFO.:	US 2001-800855	A1	20010307 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-265299, filed on 9 Mar 1999, PENDING Continuation-in-part of Ser. No. US 1998-65012, filed on 23 Apr 1998, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-77977	19980313 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ARNALL GOLDEN & GREGORY, LLP, 2800 ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, ATLANTA, GA, 30309-3450
NUMBER OF CLAIMS: 34
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 526
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Methods and compositions for treating and preventing **mucositis**

AB A method of reducing or inhibiting **mucositis** in a patient, which includes administering an inflammatory cytokine inhibitor or a mast cell inhibitor, or a combination thereof, is. . .

SUMM [0002] This invention relates to methods and compositions for treating and preventing **mucositis**.

SUMM [0003] **Mucositis** is the destruction of the oral mucosal epithelium, which results in erythema, ulcerations and severe pain in the oral cavity. **Mucositis** often arises as a complication of antineoplastic therapy, such as cancer chemotherapy and/or radiation therapy. The painful ulcerative lesions of **mucositis** can cause patients to restrict their oral intake; as a result, they lose weight and suffer from fever associated with dehydration. Severe **mucositis** can necessitate the de-escalation of a planned chemo/radio-therapeutic dosing regimen to prevent further damage to the oral mucosa.

SUMM [0004] An even more serious consequence of **mucositis** is that the lesions can act as sites of secondary infections and as portals of entry for endogenous oral microorganisms. **Mucositis** is therefore a significant risk factor for life-threatening systemic infection (septicemia); the risk of systemic infection is exacerbated by concomitant neutropenia, which is another complication associated with chemotherapy. Patients with **mucositis** and neutropenia have a relative risk of septicemia that is at least four times greater than that of individuals without **mucositis**.

SUMM [0005] The overall frequency of **mucositis** varies; it is influenced by the patient's diagnosis, age, and level of oral health, as well as the type, dose,. . . and frequency of drug or radiation administration. Approximately 40% of all patients who receive cancer chemotherapy suffer some degree of **mucositis**, and virtually 100% of patients treated with radiation therapy for head and neck tumors develop **mucositis**. The frequency of severe **mucositis** in patients undergoing high risk protocols is over 60%. About 50% of individuals develop lesions severe enough to require modification. . .

SUMM [0006] The development of effective methods for treating and preventing **mucositis** has been hampered by a lack of understanding of the pathophysiology of this condition, and by the inconsistency in patient. . .

SUMM [0007] The invention features methods for treating and preventing **mucositis**. The invention is based, in part, on the recognition that **mucositis** is a complex biological process resulting from the cumulative and interactive effects of radiation and/or chemotherapy with epithelial connective tissue. . .

SUMM [0008] We hypothesize that **mucositis** represents a clinical outcome due to a complex interaction of local tissue (connective tissue, endothelium, epithelium) toxicity, the level of. . .

SUMM . . . inflammatory cells expressing pro-inflammatory cytokines occurs during the breakdown of the mucosa and peaks just prior to the acme of **mucositis**. Bacterial colonization of the damaged epithelium occurs and is accelerated by the patient's myelosuppressed state. Typically the nadir follows a day or so after peak **mucositis**. Bacterial cell wall products from both gram positive and gram negative organisms likely then penetrate the injured mucosa and further. . .

SUMM [0010] According to the invention, **mucositis** can be treated, or even prevented, by the administration of inflammatory cytokine inhibitors, MMP inhibitors, and/or mast cell inhibitors. The. . . these inhibitors with an anti-inflammatory agent and/or an antimicrobial agent provides an even more effective regime for preventing and treating

mucositis.

SUMM [0011] The invention features a method of reducing or inhibiting **mucositis**, in a patient suffering from **mucositis** or at risk for **mucositis**; the method includes administering to the patient a first therapeutic agent in an amount sufficient to inhibit **mucositis**, where the first therapeutic agent is an inflammatory cytokine inhibitor, a mast cell inhibitor, an MMP inhibitor, or a combination. . . A preferred MMP inhibitor is a tetracycline such as minocycline, which used by itself in low doses is an effective **mucositis** agent that does not primarily act as an antibiotic. Other members of the tetracycline family can be used as well, e.g., chlortetracycline and oxytetracycline. An example of a **mucositis** that can be reduced or inhibited according to the invention is oral **mucositis**.

SUMM [0012] The invention also features a method of treating, inhibiting, or preventing **mucositis** in the human patient by administering to the patient first and second different therapeutic agents, the first agent being an. . . as a tetracycline, eg, minocycline. Exemplary NO inhibitors are aminoguanidine and guanidine. Another TNF-alpha inhibitor that can be used is **thalidomide**. Mast cell inhibitors can be antihistamines, serine protease inhibitors, or degranulation inhibitors.

SUMM [0014] In another preferred method, the first therapeutic agent, in an amount sufficient to inhibit **mucositis**, and the third therapeutic agent, in an amount sufficient to inhibit infection, are administered. Preferably, the first therapeutic agent and. . .

SUMM [0015] The **mucositis** being treated can be induced by antineoplastic therapy; for example, it can be induced by chemotherapy or by radiation therapy.. . .

SUMM [0016] The invention further features a pharmaceutical composition for treating oral **mucositis** that includes (a) a first therapeutic agent including an inflammatory cytokine inhibitor, a mast cell inhibitor, an MMP inhibitor or. . . agent; and (c) a pharmaceutically acceptable carrier. The first and second therapeutic agents are present in amounts sufficient to inhibit **mucositis** in a patient suffering from **mucositis** or at risk for **mucositis**. Preferably, the composition is formulated into a lozenge, a tablet, an oral rinse, an oral paste, or an oral gel.. . .

DRWD [0017] FIG. 1 is a schematic representation illustrating the four phases of **mucositis** development and resolution.

DETD [0018] The invention features methods and compositions for reducing and inhibiting **mucositis** that include administering inflammatory cytokine inhibitors and/or mast cell inhibitors.

DETD [0019] The invention is based, in part, on the development of a new mechanistic scheme for the physiological basis of **mucositis**. According to this scheme, the development and resolution of **mucositis** occurs in four interrelated phases: (i) an inflammatory/vascular response; (ii) a degenerative connective tissue and/or epithelial phase; (iii) an ulcerative/bacteriological. . .

DETD . . . in the local levels of cytotoxic agents. Both IL-1 and TNF-.alpha. cause local tissue damage, and thereby initiate and accelerate **mucositis**.

DETD . . . also based, in part, on the discovery that proliferation of mast cells plays a key role in the development of **mucositis**. Mast cells are granule-containing secretory cells which are present in mucosal and connective tissues, and which can migrate within these. . .

DETD . . . the mast cells or the action of the mediators released by mast cells can be used to treat and prevent **mucositis**. Mast cell

inhibitors are chemical or biological agents that suppress or inhibit the function of mast cells, or the mediators. . .

DETD [0034] According to the invention, inflammatory cytokine inhibitors can also be used to treat and prevent **mucositis**. Inflammatory cytokine inhibitors are chemical or biological agents that suppress or inhibit inflammatory cytokines. Such inhibitors include pyridinyl imidazoles, bicyclic imidazoles, oxpentifylline, **thalidomide** and gabexate mesilate.

DETD [0035] Anti-inflammatory agents can be used in combination with inflammatory cytokine and/or mast cell inhibitors to treat and prevent **mucositis** according to the invention. Examples of anti-inflammatory agents that can be used in the present invention include the non-steroidal anti-inflammatory. . .

DETD . . . for the elevated production of prostaglandins during inflammation. COX-2 inhibitors are especially useful where the invention is used to treat **mucositis** in cancer patients undergoing chemotherapy or radiation therapy, because of the gastrointestinal tolerability of these inhibitors. COX-2 inhibitors that can. . .

DETD . . . agents in combination with the agents described above can result in an even more effective method for treating and preventing **mucositis**. Examples of antimicrobial agents that can be used include agents with spectrum for gram positive and gram negative organisms. Specific. . .

DETD [0041] Other agents that can be used to treat or prevent **mucositis** include the nuclear transcription factor kappa-B (NF-.kappa.B) activation inhibitors capsaicin and resiniferatoxin.

DETD [0044] Since the compositions of the invention can help prevent **mucositis**, administration of the compositions should preferably precede the initial dose of antineoplastic therapy by at least 24 hours. Daily treatment. . .

DETD [0059] For treatment according to the methods described herein, patients are dosed with a topical application of **mucositis** medication as a troche or lozenge, beginning the evening before the first dose of chemotherapy. The lozenge contains therapeutic doses. . .

DETD . . . assure exposure of the drug to the oropharynx. The fourteen-day dosing period provides coverage through the first three phases of **mucositis** development.

DETD . . . dose of radiation of about 60 Gy, given in divided doses over a 6-week to 8-week period. Early signs of **mucositis** are noted at doses of around 10 Gy, and frank breakdown of the mucosa is seen at around 25 Gy.

DETD [0063] Beginning with the second week of this type of radiation therapy, patients receive **mucositis** medication 2 hours prior to each daily dose of radiation, which is typically given 5 days per week. Subsequent **mucositis** medication is given 2 hours, 6 hours, and 12 hours following daily radiation. Since myelosuppression is not an issue for patients being radiated for head and neck cancers, the **mucositis** preparation includes mast cell inhibitors, cytokine inhibitors, and anti-inflammatory agents, but no anti-microbial agents. Patients do not receive **mucositis** medication on days on which they are not radiated. The protocol is followed until radiation dosing is completed.

DETD . . . specific anti-cancer drugs for treatment of this form of tumor, this group of patients is at particular risk for developing **mucositis**. Patients in this group begin dosing with **mucositis** medication two hours prior to chemotherapy administration. They continue taking **mucositis** medication every 4 hours, while awake, for at least the next 48 hours. The regimen

is repeated for each dosing. . .

DETD . . . to treat and prevent conditions such as lichen planus and graft-vs-host disease, which have similar biological mechanisms to that of **mucositis**.

CLM What is claimed is:

1. A method of treating, inhibiting, or preventing **mucositis** in a human patient, said method comprising administering to said patient first and second different therapeutic agents, wherein said first. . .

10. The method of claim 1 wherein the TNF-alpha inhibitor is **thalidomide**.

15. A method of treating, inhibiting, or preventing **mucositis** in a human patient, said method comprising administering to said patient an effective amount of a therapeutic agent selected from. . .

22. The method of claim 1, wherein said **mucositis** is induced by antineoplastic therapy.

23. The method of claim 22, wherein said **mucositis** is induced by chemotherapy.

24. The method of claim 22, wherein said **mucositis** is induced by radiation therapy.

27. The method of claim 1, wherein said **mucositis** is oral **mucositis**.

28. A pharmaceutical composition for treating oral **mucositis** comprising (a) a first therapeutic agent comprising an NSAID, an inflammatory cytokine inhibitor, or a mast cell inhibitor; (b) a. . . and (c) a pharmaceutically acceptable carrier, wherein said first and second therapeutic agents are present in amounts sufficient to inhibit **mucositis** in a patient suffering from **mucositis** or at risk for **mucositis**.

L7 ANSWER 6 OF 22 USPATFULL

AB Use of benzydamine and physiologically acceptable acid addition salts thereof for preparing a medicament for the treatment of pathological conditions caused by TNF.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2001:173612 USPATFULL			
TITLE:	Use of benzydamine in the treatment of pathological conditions caused by TNF			
INVENTOR(S):	Cioli, Valerio, Roma, Italy			
PATENT ASSIGNEE(S):	Angelini Ricerche S.p.A. Societa'Consortile, S. Palomba-Pomezia, Italy (non-U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6300358	B1	20011009	
	WO 9503799		19950209	
APPLICATION INFO.:	US 1996-586804		19960506	(8)
	WO 1994-EP2343		19940714	
			19960506	PCT 371 date
			19960506	PCT 102(e) date

NUMBER DATE

PRIORITY INFORMATION:	IT 1993-MI1673	19930727
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Jones, Dwayne C.	
LEGAL REPRESENTATIVE:	Oblon, Spivak, McClelland, Maier & Neustadt, P.C.	
NUMBER OF CLAIMS:	11	
EXEMPLARY CLAIM:	1	
LINE COUNT:	234	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . is however mainly used for those diseases which involve local inflammation such as for example myalgia, tendinitis, vulvovaginitis, gingivitis, stomatitis, **mucositis** of the oral cavity and so forth.

SUMM Suramin (EP-A-0 486 809), **thalidomide** (Sampaio E. P. "J. Exp.

L7 ANSWER 7 OF 22 USPATFULL

AB In accordance with the present invention, there are provided conjugates of physiologically compatible free radical scavengers (e.g., dithiocarbamate disulfides (DD)) and pharmacologically active agents (e.g., NSAIDS). Invention conjugates provide a new class of pharmacologically active agents (e.g., anti-inflammatory agents) which cause a much lower incidence of side-effects due to the protective effects imparted by modifying the pharmacologically active agents as described herein. In addition, invention conjugates are more effective than unmodified pharmacologically active agents because cells and tissues contacted by the pharmacologically active agent(s) are protected from the potentially damaging effects of free radical overproduction induced thereby as a result of the co-production of free radical scavenger (e.g., dithiocarbamate), in addition to free pharmacologically active agent, when invention conjugate is cleaved.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2001:131342 USPATFULL		
TITLE:	Conjugates of dithiocarbamate disulfides with pharmacologically active agents and uses therefor		
INVENTOR(S):	Lai, Ching-San, Encinitas, CA, United States Vassilev, Vassil P., San Diego, CA, United States Wang, Tingmin, San Marcos, CA, United States		
PATENT ASSIGNEE(S):	Medinox, Inc., San Diego, CA, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6274627	B1	20010814
APPLICATION INFO.:	US 1999-416619		19991012 (9)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Weddington, Kevin E.		
LEGAL REPRESENTATIVE:	Reiter, Stephen E.Foley & Lardner		
NUMBER OF CLAIMS:	9		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 5 Drawing Page(s)		
LINE COUNT:	2173		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . Gianni et al., in Rev. Biochem. Toxicol. 5:1-82 (1983)). In addition to cardiomyopathy, adriamycin administration causes cutaneous irritation and alopecia, **mucositis** (stomatitis and

esophagitis), phlebosclerosis and hematologic toxicities and many other local and systemic toxicities.

DETD antimetabolite cytotoxics (azathioprine, cyclophosphamide), C5a release inhibitor, benzydamine, peldesine, pentostatin, SDZ-ASM-981, **thalidomide**, benzoporphyrin derivatives, arachidonate antagonists (e.g., halometasone, halobetasol propionate), corticosteriod (clobetasol propionate), growth hormone antagonists (octapeptide somatostatin analogue, lanreotide, angiopeptin and. . .

DETD . . . (e.g., BTI-322), campath-1H, CD4 antagonist (e.g., CE9.1 and SB-210396), tumor necrosis factor antagonist (e.g., p80 TNFR, rhTNFbp, peptide T, CenTNF, **thalidomide**, CDP-571 and TBP-1), cobra venom factor, interleukin 1a agonist (e.g., cytogenin), interleukin 2 receptor antagonist (e.g., dacliximab), ICAM 1 antagonist. . .

DETD . . . antagonists (e.g., lectin-1, and recombinant IML-1), soluble TNF receptor I, TCARs (e.g., TCR, CD3/Ti, and peptigen TP12), TNF antagonists (e.g., **thalidomide**, and TNF inhibitors), tricyclic antidepressants, and the like;

L7 ANSWER 8 OF 22 CAPLUS COPYRIGHT 2002 ACS

AB This review summarises the large no. of locally and systemically applied preventive and therapeutic interventions of **mucositis** in patients with cancer. The need for further elucidation of the pathophysiol. and for optimization of trial methodol. is emphasized. Data from trials in animal models and preliminary data in patients indicate that cytokines such as interleukin-1, interleukin-11, TGF-.beta.3 and keratinocyte growth factor could reduce the incidence of **mucositis** . Other potentially useful agents are the angiogenesis-inhibiting drug **thalidomide**, the cytoprotector amifostine and the pineal hormone melatonin.

ACCESSION NUMBER:	2000:816317 CAPLUS
TITLE:	Prevention and management of **mucositis** in patients with cancer
AUTHOR(S):	Herrstedt, Jorn
CORPORATE SOURCE:	Department of Oncology, Copenhagen University Hospital, Herlev, DK-2730, Den.
SOURCE:	Int. J. Antimicrob. Agents (2000), 16(2), 161-163 CODEN: IAAGEA; ISSN: 0924-8579
PUBLISHER:	Elsevier Science Ireland Ltd.
DOCUMENT TYPE:	Journal
LANGUAGE:	English
REFERENCE COUNT:	14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Prevention and management of **mucositis** in patients with cancer

AB This review summarises the large no. of locally and systemically applied preventive and therapeutic interventions of **mucositis** in patients with cancer. The need for further elucidation of the pathophysiol. and for optimization of trial methodol. is emphasized. Data from trials in animal models and preliminary data in patients indicate that cytokines such as interleukin-1, interleukin-11, TGF-.beta.3 and keratinocyte growth factor could reduce the incidence of **mucositis** . Other potentially useful agents are the angiogenesis-inhibiting drug **thalidomide**, the cytoprotector amifostine and the pineal hormone melatonin.

L7 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2002 ACS

AB A method of reducing or inhibiting **mucositis** in a patient includes administering an inflammatory cytokine inhibitor or a mast cell inhibitor, or a combination thereof.

ACCESSION NUMBER: 1999:594911 CAPLUS
DOCUMENT NUMBER: 131:209126
TITLE: Methods and compositions using inflammatory cytokine inhibitors and mast cell inhibitors for treating and preventing **mucositis**
INVENTOR(S): Sonis, Stephen T.; Fey, Edward G.
PATENT ASSIGNEE(S): Mucosal Therapeutics Llc, USA
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9945910	A2	19990916	WO 1999-US5437	19990312
WO 9945910	A3	20000210		
W: AU, BR, CA, IL, JP, MX, NZ, PL				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9930837	A1	19990927	AU 1999-30837	19990312
BR 9908857	A	20001031	BR 1999-8857	19990312
EP 1064001	A2	20010103	EP 1999-912467	19990312
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 2001011097	A1	20010802	US 2001-800855	20010307

PRIORITY APPLN. INFO.:
US 1998-77977 P 19980313
US 1998-65012 A 19980423
US 1999-265299 A 19990309
WO 1999-US5437 W 19990312

TI Methods and compositions using inflammatory cytokine inhibitors and mast cell inhibitors for treating and preventing **mucositis**

AB A method of reducing or inhibiting **mucositis** in a patient includes administering an inflammatory cytokine inhibitor or a mast cell inhibitor, or a combination thereof.

ST inflammatory cytokine inhibitor **mucositis** treatment; mast cell inhibitor **mucositis** treatment

IT Mucous membrane
(disease, inflammation; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Drug delivery systems
(gels, oral; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Anti-inflammatory agents
Antihistamines
Antimicrobial agents
Antiulcer agents
Drug delivery systems
Mast cell
Mouthwashes
(inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Cytokines
Interleukin 1
Interleukin 6
Tumor necrosis factors

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Tetracyclines
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Drug delivery systems
(lozenges; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Cell degranulation
(mast cell, inhibitors; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Stomach, disease
(mucosa, injury; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Antitumor agents
Chemotherapy
Radiotherapy
(**mucositis** induced by; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Inflammation
(mucous membrane; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Anti-inflammatory agents
(nonsteroidal; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Drug delivery systems
(oral; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Drug delivery systems
(pastes, oral; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Mouth
(stomatitis; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Drug delivery systems
(tablets; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Interferons
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(.gamma.; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT 39391-18-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(1 and 2, inhibitors; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT 50-35-1, **Thalidomide** 53-86-1, Indomethacin 79-17-4, Aminoguanidine 113-00-8, Guanidine 5104-49-4, Flurbiprofen 10118-90-8, Minocycline

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT 10102-43-9, Nitric oxide, biological studies 37259-58-8, Serine protease 141907-41-7, Matrix metalloproteinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

L7 ANSWER 10 OF 22 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 1999:124900 USPATFULL
TITLE: Enantiomerically pure hydroxylated xanthine compounds
INVENTOR(S): Bianco, James A., Seattle, WA, United States
Woodson, Paul, Bothell, WA, United States
Porubek, David, Edmonds, WA, United States
Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5965564		19991012
APPLICATION INFO.:	US 1998-44976		19980320 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-457703, filed on 1 Jun 1995, now patented, Pat. No. US 5739138 which is a division of Ser. No. US 1994-343810, filed on 22 Nov 1994, now patented, Pat. No. US 5652243 which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994, now patented, Pat. No. US 5648357 which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1770

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . isomer, which usually has no therapeutic value and has the potential to cause unsuspected side effects. For example, the sedative **thalidomide** was marketed as a racemate. The desired sedative activity resided in the R-isomer, but the contaminating S-isomer is a teratogen,. . .

DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

CLM What is claimed is:
5. The method of claim 1, wherein the treating or preventing infection decreases the incidence or severity of **mucositis** in the patient.

L7 ANSWER 11 OF 22 USPATFULL

AB In accordance with the present invention, there are provided conjugates of nitric oxide scavengers (e.g., dithiocarbamates, or "DC") and pharmacologically active agents (e.g., NSAIDs). Invention conjugates provide a new class of pharmacologically active agents (e.g., anti-inflammatory agents) which cause a much lower incidence of side-effects due to the protective effects imparted by modifying the pharmacologically active agents as described herein. In addition, invention conjugates are more effective than unmodified pharmacologically active agents because cells and tissues contacted by the pharmacologically active agent(s) are protected from the potentially damaging effects of nitric oxide overproduction induced thereby as a result of the co-production of nitric oxide scavenger (e.g., dithiocarbamate), in addition to free pharmacologically active agent, when invention conjugate is cleaved.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1999:72602 USPATFULL		
TITLE:	Conjugates of dithiocarbamates with pharmacologically active agents and uses therefore		
INVENTOR(S):	Lai, Ching-San, Encinitas, CA, United States		
PATENT ASSIGNEE(S):	Medinox, Inc., San Diego, CA, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5916910		19990629
APPLICATION INFO.:	US 1997-869158		19970604 (8)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Davis, Zinna Northington		
LEGAL REPRESENTATIVE:	Reiter, Esq., Stephen E.Gray, Cary, Ware & Freidenrich		
NUMBER OF CLAIMS:	27		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1842		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . Gianni et al., in Rev. Biochem. Toxicol. 5:1-82 (1983)). In addition to cardiomyopathy, adriamycin administration causes cutaneous irritation and alopecia, **mucositis** (stomatitis and esophagitis), phlebosclerosis and hematologic toxicities and many other local and systemic toxicities.

SUMM antimetabolite cytotoxics (azathioprine, cyclophosphamide), C5a release inhibitor, benzydamine, peldesine, pentostatin, SDZ-ASM-981, **thalidomide**, benzoporphyrin derivatives, arachidonate antagonists (e.g., halometasone, halobetasol propionate), corticosteriod (clobetasol propionate), growth hormone antagonists (octapeptide

somatostatin analogue, lanreotide, angiopeptin and. . .
SUMM . . . (e.g., BTI-322), campath-1H, CD4 antagonist (e.g., CE9.1 and SB-210396), tumor necrosis factor antagonist (e.g., p80 TNFR, rhTNFbp, peptide T, CenTNF, **thalidomide**, CDP-571 and TBP-1), cobra venom factor, interleukin 1a agonist (e.g., cytogenin), interleukin 2 receptor antagonist (e.g., dacliximab), ICAM 1 antagonist. . .
SUMM . . . antagonists (e.g., lectin-1, and recombinant IML-1), soluble TNF receptor I, TCARs (e.g., TCR, CD3/Ti, and peptigen TP12), TNF antagonists (e.g., **thalidomide**, and TNF inhibitors), tricyclic antidepressants, and the like;

L7 ANSWER 12 OF 22 USPATFULL
AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 1998:95545 USPATFULL
TITLE: Enatiomerically pure hydroxylated xanthine compounds
INVENTOR(S): Bianco, James A., Seattle, WA, United States
Woodson, Paul, Bothell, WA, United States
Porubek, David, Edmonds, WA, United States
Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5792772		19980811
APPLICATION INFO.:	US 1995-458957		19950601 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994, now patented, Pat. No. US 5652243 which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994, now patented, Pat. No. US 5648357 which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1734
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . isomer, which usually has no therapeutic value and has the potential to cause unsuspected side effects. For example, the sedative **thalidomide** was marketed as a racemate. The desired sedative activity resided in the R-isomer, but the contaminating S-isomer is a teratogen,. . .
DETD . . . disorder, a neurological disorder, an autoimmune disease,

inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

L7 ANSWER 13 OF 22 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1998:39529 USPATFULL
TITLE:	Enantiomerically pure hydroxylated xanthine compounds to treat autoimmune diabetes
INVENTOR(S):	Bianco, James A., Seattle, WA, United States Woodson, Paul, Bothell, WA, United States Porubek, David, Edmonds, WA, United States Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5739138		19980414
APPLICATION INFO.:	US 1995-457703		19950601 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994, now abandoned which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994, now abandoned which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Criares, Theodore J.
LEGAL REPRESENTATIVE:	Faciszewski, Stephen
NUMBER OF CLAIMS:	2
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT:	1734

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . isomer, which usually has no therapeutic value and has the potential to cause unsuspected side effects. For example, the sedative **thalidomide** was marketed as a racemate. The desired sedative activity resided in the R-isomer, but the contaminating S-isomer is a teratogen,. . .

DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

L7 ANSWER 14 OF 22 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	97:66130 USPATFULL
TITLE:	Methods of using enantiomerically pure hydroxylated xanthine compounds
INVENTOR(S):	Bianco, James A., Seattle, WA, United States Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5652243		19970729
APPLICATION INFO.:	US 1994-343810		19941122 (8)

RELATED APPLN. INFO.:	Division of Ser. No. US 1994-307554, filed on 16 Sep 1994 which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned
DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Criares, Theodore J.
LEGAL REPRESENTATIVE:	Oster, Jeffrey B., Faciszewski, Stephen
NUMBER OF CLAIMS:	4
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT:	1731

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . isomer, which usually has no therapeutic value and has the potential to cause unsuspected side effects. For example, the sedative **thalidomide** was marketed as a racemate. The desired sedative activity resided in the R-isomer, but the contaminating S-isomer is a teratogen,. . .

DETD . . . hormone-related disorder, a neurological disorder, an autoimmune disease/inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

CLM What is claimed is:

4. The method of claim 1 wherein the organ toxicity is gastrointestinal **mucositis**.

L7 ANSWER 15 OF 22 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in

modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	97:61689 USPATFULL
TITLE:	Enatiomerically pure hydroxylated xanthine compounds
INVENTOR(S):	Bianco, James A., Seattle, WA, United States Woodson, Paul, Bothell, WA, United States Porubek, David, Edmonds, WA, United States Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5648357		19970715
APPLICATION INFO.:	US 1994-307554		19940916 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Criares, Theodore J.
LEGAL REPRESENTATIVE:	Oster, Jeffrey B., Faciszewski, Stephen
NUMBER OF CLAIMS:	10
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT:	1748

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . isomer, which usually has no therapeutic value and has the potential to cause unsuspected side effects. For example, the sedative **thalidomide** was marketed as a racemate. The desired sedative activity resided in the R-isomer, but the contaminating S-isomer is a teratogen,. . .

DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

L7 ANSWER 16 OF 22 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	97:40793 USPATFULL
TITLE:	Treatment of diseases using enantiomerically pure hydroxylated xanthine compounds
INVENTOR(S):	Bianco, James A., Seattle, WA, United States

	Woodson, Paul, Bothell, WA, United States
	Porubek, David, Edmonds, WA, United States
	Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5629315		19970513
APPLICATION INFO.:	US 1995-456900		19950601 (8)

DISCLAIMER DATE: 20150601
RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994, now abandoned which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994, now abandoned which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: Faciszewski, Stephen
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1736
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . isomer, which usually has no therapeutic value and has the potential to cause unsuspected side effects. For example, the sedative **thalidomide** was marketed as a racemate. The desired sedative activity resided in the R-isomer, but the contaminating S-isomer is a teratogen,. . .
DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

L7 ANSWER 17 OF 22 USPATFULL
AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 97:31820 USPATFULL
TITLE: Process for preparing enantiomerically pure xanthine derivatives
INVENTOR(S): Bianco, James A., Seattle, WA, United States
Woodson, Paul, Bothell, WA, United States
Porubek, David, Edmonds, WA, United States
Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States

(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5621102		19970415
APPLICATION INFO.:	US 1995-456897		19950601 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994, now abandoned which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994, now abandoned which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Rotman, Alan L.
LEGAL REPRESENTATIVE: Faciszewski, Stephen
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1763
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . isomer, which usually has no therapeutic value and has the potential to cause unsuspected side effects. For example, the sedative **thalidomide** was marketed as a racemate. The desired sedative activity resided in the R-isomer, but the contaminating S-isomer is a teratogen,. . .

DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

L7 ANSWER 18 OF 22 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in treating inflammatory disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 97:31706 USPATFULL
TITLE: Enatiomerically pure hydroxylated xanthine compounds to treat inflammatory diseases
INVENTOR(S): Bianco, James A., Seattle, WA, United States
Woodson, Paul, Bothell, WA, United States
Porubek, David, Edmonds, WA, United States
Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5620984		19970415
APPLICATION INFO.:	US 1995-456898		19950601 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov

1994 which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994 which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: Faciszewski, Stephen, Oster, Jeffrey B.
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1721
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . isomer, which usually has no therapeutic value and has the potential to cause unsuspected side effects. For example, the sedative **thalidomide** was marketed as a racemate. The desired sedative activity resided in the R-isomer, but the contaminating S-isomer is a teratogen,. . .

DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

L7 ANSWER 19 OF 22 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 97:22792 USPATFULL
TITLE: Enantiomerically pure hydroxylated xanthine compounds to treat shock symptoms
INVENTOR(S): Bianco, James A., Seattle, WA, United States
Woodson, Paul, Bothell, WA, United States
Porubek, David, Edmonds, WA, United States
Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5612349		19970318
APPLICATION INFO.:	US 1995-457062		19950601 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994, now abandoned which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994, now abandoned which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now

abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: Faciszewski, Stephen
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1725
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . isomer, which usually has no therapeutic value and has the potential to cause unsuspected side effects. For example, the sedative **thalidomide** was marketed as a racemate. The desired sedative activity resided in the R-isomer, but the contaminating S-isomer is a teratogen,. . .
DRWD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

L7 ANSWER 20 OF 22 USPATFULL
AB Them is disclosed compounds and pharmaceutical compositions that is R enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in treating the side effects of immunosuppressive agent and interleukin-2 therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 96:111463 USPATFULL
TITLE: Enatiomerically pure hydroxylated xanthine compounds
INVENTOR(S): Bianco, James A., Seattle, WA, United States
Woodson, Paul, Bothell, WA, United States
Porubek, David, Edmonds, WA, United States
Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5580874		19961203
APPLICATION INFO.:	US 1995-457685		19950601 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994, now abandoned which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994 which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: Faciszewski, Stephen
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1733
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . isomer, which usually has no therapeutic value and has the potential to cause unsuspected side effects. For example, the sedative **thalidomide** was marketed as a racemate. The desired sedative activity resided in the R-isomer, but the contaminating S-isomer is a teratogen,. . .
DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

L7 ANSWER 21 OF 22 USPATFULL
AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in treating proliferative vascular disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 96:111462 USPATFULL
TITLE: Enatiomerically pure hydroxylated xanthine compounds to treat proliferative vascular diseases
INVENTOR(S): Bianco, James A., Seattle, WA, United States
Woodson, Paul, Bothell, WA, United States
Porubek, David, Edmonds, WA, United States
Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5580873		19961203
APPLICATION INFO.:	US 1995-456899		19950601 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994 which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994 which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: Oster, Jeffrey B.
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1728
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . isomer, which usually has no therapeutic value and has the potential to cause unsuspected side effects. For example, the sedative **thalidomide** was marketed as a racemate. The desired sedative activity resided in the R-isomer, but the contaminating S-isomer is a

teratogen,. . .

DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

L7 ANSWER 22 OF 22 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in treating baldness.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 96:97041 USPATFULL

TITLE: R-enatiomerically pure hydroxylated xanthine compounds to treat baldness

INVENTOR(S): Bianco, James A., Seattle, WA, United States
Woodson, Paul, Bothell, WA, United States
Porubek, David, Edmonds, WA, United States
Singer, Jack, Seattle, WA, United States

PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5567704		19961022
APPLICATION INFO.:	US 1995-457683		19950601 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994 which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994 which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: Oster, Jeffrey B.
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1736

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . isomer, which Usually has no therapeutic value and has the potential to cause unsuspected side effects. For example, the sedative **thalidomide** was marketed as a racemate. The desired sedative activity resided in the R-isomer, but the contaminating S-isomer is a teratogen,. . .

DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

```
=> s (IL(2a)1(5a)(inhibit? or antagonist?) or interferon(2a)gamma(5a)(inhibitor? or
antagonist?))
L8        7309 (IL(2A) 1(5A)(INHIBIT? OR ANTAGONIST?) OR INTERFERON(2A) GAMMA(5
               A)(INHIBITOR? OR ANTAGONIST?))

=> s l8 and mucositi?
L9          60 L8 AND MUCOSITI?

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10         60 DUP REM L9 (0 DUPLICATES REMOVED)

=> s l10 and py<=1998
L11         36 L10 AND PY<=1998

=> d l11 abs ibib kwic 1-36

L11  ANSWER 1 OF 36  CAPLUS  COPYRIGHT 2002 ACS
AB   Interleukin-11 (IL-11) is a pleiotropic cytokine that exhibits
     anti-inflammatory and mucosal protective effects in a variety of animal
     models of acute and chronic inflammation, such as mucositis,
     inflammatory bowel disease and autoimmune joint disease. This redn. in
     inflammation and epithelial damage is mediated in part through effects of
     recombinant human (rh) IL-11 on macrophage effector function and
     epithelial cell growth. In vitro studies indicate that rhIL-11
     inhibits tumor necrosis factor (TNF)-.alpha., IL-
     1.beta., IL-12, IL-6, and nitric oxide prodn. from activated
     macrophages. Anal. of the effects of rhIL-11 on transcription factors
     that activate pro-inflammatory cytokines demonstrate that the level of
     induced nuclear factor kappa B (NF-.kappa.B) binding activity in the
     nucleus of rhIL-11-treated peritoneal macrophages is significantly
     reduced. Studies of normal intestinal epithelial cells indicate that
     rhIL-11 reduces the rate of cellular proliferation. Anal. of cell-cycle
     progression demonstrates that growth inhibition of epithelial cells by
     rhIL-11 correlates with delayed entry into S phase and suppression of pRB
     phosphorylation. IL-11 also protects intestinal crypt stem cells from
     radiation- or chemotherapy-induced insults. Such immunomodulatory and
     epithelial activities may contribute to the protective effects of this
     cytokine and support the clin. utility of rhIL-11 in the treatment of
     mucositis, as well as a variety of chronic inflammatory diseases,
     such as Crohn's disease and rheumatoid arthritis.
ACCESSION NUMBER:         1998:583825  CAPLUS
TITLE:                    The therapeutic utility of Interleukin-11 in the
                          treatment of inflammatory disease
AUTHOR(S):                Trepicchio, William L.; Dorner, Andrew J.
CORPORATE SOURCE:         Department of Preclinical Molecular and Cellular
                          Biology, Genetics Institute, Andover, MA, 01810, USA
SOURCE:                   Expert Opin. Invest. Drugs (1998), 7(9),
                          1501-1504
                          CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER:                Ashley Publications
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
SO   Expert Opin. Invest. Drugs (1998), 7(9), 1501-1504
     CODEN: EOIDER; ISSN: 1354-3784
AB   Interleukin-11 (IL-11) is a pleiotropic cytokine that exhibits
```

anti-inflammatory and mucosal protective effects in a variety of animal models of acute and chronic inflammation, such as **mucositis**, inflammatory bowel disease and autoimmune joint disease. This redn. in inflammation and epithelial damage is mediated in part through effects of recombinant human (rh) IL-11 on macrophage effector function and epithelial cell growth. In vitro studies indicate that rhIL-11 **inhibits** tumor necrosis factor (TNF)-.alpha., **IL-1**.beta., IL-12, IL-6, and nitric oxide prodn. from activated macrophages. Anal. of the effects of rhIL-11 on transcription factors that activate pro-inflammatory cytokines demonstrate that the level of induced nuclear factor kappa B (NF-.kappa.B) binding activity in the nucleus of rhIL-11-treated peritoneal macrophages is significantly reduced. Studies of normal intestinal epithelial cells indicate that rhIL-11 reduces the rate of cellular proliferation. Anal. of cell-cycle progression demonstrates that growth inhibition of epithelial cells by rhIL-11 correlates with delayed entry into S phase and suppression of pRB phosphorylation. IL-11 also protects intestinal crypt stem cells from radiation- or chemotherapy-induced insults. Such immunomodulatory and epithelial activities may contribute to the protective effects of this cytokine and support the clin. utility of rhIL-11 in the treatment of **mucositis**, as well as a variety of chronic inflammatory diseases, such as Crohn's disease and rheumatoid arthritis.

L11 ANSWER 2 OF 36 USPATFULL

AB Therapeutic compounds have the formula:

(X)j-(core moiety),

j being an integer from one to three, the core moiety comprising a core moiety, the core moiety being a heterocycle having one ring or two-fused rings, each ring having five or six ring atoms, A being a carbon atom of the core moiety and attached to a terminal carbon atom of (CH.sub.2).sub.m, and X has a structure and X being a racemic mixture, R or S enantiomer, solvate, hydrate, or salt of: ##STR1## *C is a chiral carbon atom, n is an integer from one to four (preferably from one to three), one or more carbon atoms of (CH.sub.2).sub.n may be substituted by a keto or hydroxy group, and m is an integer from one to fourteen. Independently, R.sub.1 and R.sub.2 may be a hydrogen, a straight or branched chain alkyl or alkenyl of up to twelve carbon atoms in length, or --(CH.sub.2).sub.w R.sub.5, w being an integer from two to fourteen and R.sub.5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R.sub.5 being hydroxy, chloro, fluoro, bromo, or C.sub.1-6 alkoxyl. Or jointly, R.sub.1 and R.sub.2 form a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms, N being a hetero atom. R.sub.3 is a hydrogen or C.sub.1-3. Or, therapeutic compounds may also have the formula: ##STR2## R.sub.4 is a hydrogen, a straight or branched chain alkyl or alkenyl of up to eight carbon atoms in length, --(CH.sub.2).sub.w R.sub.5, w being an integer from two to fourteen and R.sub.5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R.sub.5 being hydroxy, chloro, fluoro, bromo, or C.sub.1-6 alkoxyl, or a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms, r and s are independently integers from one to four, the sum (r+s) not being greater than five. t is an integer from one to fourteen and one or more carbon atoms of (CH.sub.2).sub.s or (CH.sub.2).sub.t may be substituted by a keto or hydroxyl group.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1998:144102 USPATFULL
TITLE:	Amino-alcohol substituted cyclic compounds
INVENTOR(S):	Kumar, Anil M., Seattle, WA, United States Michnick, John, Seattle, WA, United States Underiner, Gail E., Brier, WA, United States Klein, J. Peter, Vashon Island, WA, United States Rice, Glenn C., Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5837703		19981117	<--
APPLICATION INFO.:	US 1993-152650		19931112 (8)	
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1993-40820, filed on 31 Mar 1993, now abandoned			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Raymond, Richard L.			
ASSISTANT EXAMINER:	Cebulak, Mary C.			
LEGAL REPRESENTATIVE:	Faciszewski, Stephen, Oster, Jeffrey B.			
NUMBER OF CLAIMS:	9			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	39 Drawing Figure(s); 38 Drawing Page(s)			
LINE COUNT:	2596			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5837703 19981117 <--

DRWD . . . reports inhibitive activity results for inventive compounds nos. 27, 28, 32, 30, 31, 32 and 34 in an assay measuring **inhibitive** effects in a PDGF/**IL-1** co-stimulation.

DETD . . . kidney mesengial cells; (2) suppress up-regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells; (3) **inhibit** TNF, LPS and **IL-1** induced metalloproteases (an inflammation model); (4) block LPS, TNF or IL-1 induced metalloprotease and secondary cytokine production (for prevention and. . .

DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by. . .

DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A recent review article entitled "The Role of Interleukin-1 in Disease" (Dinarello et al., N. Engl. J. Med. (1993) 106:328). . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.

DETD . . . molecules that have a role in homeostasis. The present inventive compounds address the need identified by Dinarello and Wolff by **inhibiting** cellular signaling only through the **IL-1** Type I receptor and not through the IL-1 Type II receptor.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . with ulcerative colitis, and tissue concentrations of IL-1 and IL-8 are high in patients with inflammatory bowel disease. Therefore, an **IL-1 antagonist**, such as the inventive compounds, would be effective to treat inflammatory bowel disease.

DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

DETD . . . the antitumor effect of a non-alkylating antitumor agent; (18) to inhibit the production of osteoclast activating factor in response to **IL-1**; (19) **inhibit** degranulation in response to IgE; (20) enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter,. . .

DETD . . . an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response (such as allograft reactions), viral infection, nephritis, **mucositis**, and various allergic responses. Allergic responses include acute allergic response and thus rhinorrhea, sinus drainage, diffuse tissue edema, and generalized. . .

DETD In an assay measuring **inhibitive** effects in a PDGF/**IL -1** co-stimulation, proliferation assay, a group of inventive compounds showed **inhibitive** properties. The PDGF/**IL-1** assay is useful in measuring in vitro activity, indicative of therapeutic potential for treating or preventing restenosis and reperfusion. FIG.. . .

L11 ANSWER 3 OF 36 USPATFULL

AB Disclosed are compounds having a straight or branched aliphatic hydrocarbon structure of formula I: ##STR1## In formula I, n is an integer from one to four and m is an integer from four to twenty. Independently, R.sub.1 and R.sub.2 are hydrogen, a straight or branched chain alkyl, alkenyl or alkynyl of up to twenty carbon atoms in length or --(CH.sub.2).sub.w R.sub.5. If R.sub.1 or R.sub.2 is --(CH.sub.2).sub.w R.sub.5, w may be an integer from one to twenty and R.sub.5 may be an hydroxyl, halo, C.sub.1-8 alkoxyl group or a substituted or unsubstituted carbocycle or heterocycle. Alternatively, R.sub.1 and R.sub.2 may jointly form a substituted or unsubstituted, saturated or unsaturated heterocycle having from four to eight carbon atoms, N being a hetero atom of the resulting heterocyle. R.sub.3 may be either hydrogen or C.sub.13. In the compounds, a total sum of carbon atoms comprising R.sub.1 or R.sub.2, (CH.sub.2).sub.n and (CH.sub.2).sub.m does not exceed forty. R.sub.4 is a hetorocycle comprising a substituted or unsubstituted, oxidized or reduced ring system, the ring system having a single ring or two to three fused rings, a ring comprising from three to seven ring atoms. The disclosed compounds are effective agents to inhibit undesirable responses to cell stimuli.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 1998:128265 USPATFULL

TITLE: Substituted amino alcohol compounds

INVENTOR(S): Klein, J. Peter, Vashon, WA, United States

Underiner, Gail E., Brier, WA, United States
Kumar, Anil M., Seattle, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5824677		19981020	<--
APPLICATION INFO.:	US 1995-474816		19950607 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1994-303842, filed on 8 Sep 1994, now patented, Pat. No. US 5641783 which is a continuation-in-part of Ser. No. US 1993-152650, filed on 12 Nov 1993, now patented, Pat. No. US 5801181 And Ser. No. US 1993-164081, filed on 8 Dec 1993, now patented, Pat. No. US 5470878 , said Ser. No. US -152650 And Ser. No. US -164081 , each Ser. No. US - which is a continuation-in-part of Ser. No. US 1993-40820, filed on 31 Mar 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Raymond, Richard L.
ASSISTANT EXAMINER: Cebulak, Mary C.
LEGAL REPRESENTATIVE: McDermott, Will & Emery, Faciszewski, Esq., Stephen
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 120 Drawing Figure(s); 89 Drawing Page(s)
LINE COUNT: 3136
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5824677 19981020 <--

SUMM . . . not limited to acute toxicity due to effects on rapid-proliferating tissues, such as bone marrow and oral epithelium, myelosuppression and **mucositis**, renal failure and neurological, hepatic or pulmonary toxicity. Thus, for example, a cancer therapy which effectively prevented, reduced or eliminated. . .

DRWD . . . 14 reports inhibitive activity results for compounds nos. 27, 28, 29, 30, 31, 32 and 34 in an assay measuring **inhibitive** effects in a PDGF/**IL-1**.beta. co-stimulation.

DETD . . . kidney mesangial cells; (2) suppress up-regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells; (3) **inhibit** TNF.alpha., LPS and **IL-1** .beta., induced metalloproteases (an inflammation and cancer metasteses model); (4) block LPS, TNF.alpha. or IL-1.beta. induced secondary cytokine production (for prevention. . .

DETD . . . IV collagenase that is usually constitutively produced and stimulated by TNF.alpha. or IL-1.beta., and a stromelysin/PUMP-1 induced by TNF.alpha. and **IL-1**.beta.. The inventive compounds can **inhibit** TNF.alpha. or **IL-1** .beta. induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by. . .

DETD The inventive compounds **inhibit IL-1** signal transduction, and are therefore considered as **IL-1 antagonists**. A review article entitled "Mechanisms of Disease: The Role of Interleukin-1 in Disease" (Dinarello et al., N. Engl. J. Med.,. . . disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds are **IL-1** **antagonists**, the inventive compounds are useful for treating all

of the above-mentioned diseases.

DETD . . . of molecules that have a role in homeostasis. The present inventive compounds address the need identified by Dinarello et al. **inhibiting IL-1** cellular signaling.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . with ulcerative colitis, and tissue concentrations of IL-1.beta. and IL-8 are high in patients with inflammatory bowel disease. Therefore, an **IL-1 antagonist**, such as the inventive compounds, is effective to treat inflammatory bowel disease.

DETD . . . IL-1.beta. also stimulates production of PDGF. Taken together, IL-1.beta. plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1**.beta. **antagonist**, such as the inventive compounds is useful in preventing and treating atherosclerosis.

DETD . . . the antitumor effect of a non-alkylating antitumor agent; (15) to inhibit the production of osteoclast activating factor in response to **IL-1**.beta. (16) **inhibit** degranulation in response to IgE; (17) enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter,. . .

DETD In an assay measuring **inhibitive** effects in a PDGF/**IL -1** co-stimulation,. proliferation assay, a group of compounds showed **inhibitive** properties. The PDGF/**IL-1** .beta. assay is useful in measuring in vitro activity, indicative of therapeutic potential for treating or preventing restenosis and reperfusion. FIG.. . .

DETD . . . amount of fluorescence remaining analyzed on a fluorescence plate reader. The results, reported in FIGS. 62A and 62B (TNF.alpha. or **IL-1**.beta., respectively), show **inhibition** of THP-1 adhesion to HUVEC.

DETD This example illustrates an ability of the compounds to **inhibit** both **IL-1**.alpha. or **IL**-6-stimulated proliferation of D10(N4)M or B9 cells, respectively. Using procedures similar to those discussed in the foregoing examples, cultures of D10(N4)M. . .

L11 ANSWER 4 OF 36 USPATFULL

AB Therapeutic compounds with at least one carboxylic acid, ester or amide-substituted side chain have the formula:

CORE MOIETY--(R).sub.j

wherein j is an integer from one to three. The core moiety is non-cyclic or cyclic (carbocyclic or heterocyclic). R may be selected from among hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(2-10) alkenyl, carbocyclic or heterocyclic groups and at least one R has the formula I: ##STR1## wherein: one or two p are the integer one, otherwise p is two; and n is an integer from three to twenty; R.sub.1 is selected from the group consisting of substituted and unsubstituted CH.sub.2 ; NR.sub.3, R.sub.3 being hydrogen, substituted or unsubstituted C.sub.(1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl or C.sub.(1-20) hydroxyalkyl, or carbocyclic or heterocyclic group; O; --CHR.sub.4 O--, R.sub.4 being

substituted or unsubstituted C.sub.(1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl, C.sub.(1-20) hydroxyalkyl, or R.sub.2 and R.sub.4 join to form a substituted or unsubstituted heterocycle having four to seven ring atoms, the ether group --O-- of --CHR.sub.4 O-- being a member of the heterocycle. R.sub.2 is selected from the group consisting of hydrogen; halogen; substituted or unsubstituted C.sub.(1-10) alkyl; C.sub.(1-10) alkoxyl; C.sub.(2-10) alkenyl; C.sub.(1-10) hydroxyalkyl; --A(R.sub.5).sub.m, A being N or O, m being one or two and R.sub.5 being hydrogen, a substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(1-10) alkoxyl, C.sub.(2-10) alkenyl or C.sub.(1-10) hydroxyalkyl), or carbocyclic or heterocyclic group. At least one of R.sub.1 is NR.sub.3, O or --CHR.sub.4 O--, or R.sub.2 is --A(R.sub.5).sub.m. The compounds and pharmaceutical compositions thereof are useful as therapies for diseases advanced via intracellular signaling through specific intracellular signaling pathways by mediating a signaling response to an external stimuli.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1998:111942 USPATFULL
TITLE:	Therapeutic compounds containing pyrimidinyl moieties
INVENTOR(S):	Klein, J. Peter, Vashon, WA, United States Leigh, Alistair J., Brier, WA, United States Underiner, Gail E., Brier, WA, United States Kumar, Anil M., Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5807862		19980915	<--
APPLICATION INFO.:	US 1995-478112		19950607 (8)	
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1994-199368, filed on 18 Feb 1994, now abandoned			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Gupta, Yogendra N.			
LEGAL REPRESENTATIVE:	McDermott, Will & Emery			
NUMBER OF CLAIMS:	6			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 5 Drawing Page(s)			
LINE COUNT:	2190			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5807862 19980915 <--

DETD . . . kidney mesengial cells; (2) suppress up-regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells; (3) **inhibit** TNF, LPS and **IL-1** induced metalloproteases (an inflammation model); (4) block LPS, TNF or IL-1 induced metalloprotease and secondary cytokine production (for prevention and. . .

DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysinPUMP-1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by. . .

DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A recent review article entitled "The

Role of Interleukin-1 in Disease" (Dinarello et al., N. Engl. J. Med. 328, 106,. . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.

DETD . . . molecules that have a role in homeostasis. The present inventive compounds address this need, identified by Dinarello et al., by **inhibiting** cellular signaling only through the **IL** -1 Type I receptor and not through the IL-1 Type II receptor.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . correlate to severity of disease in patients with ulcerative colitis, patients with inflammatory bowel disease having high tissue concentrations of IL-**1** and **IL**-8. Therefore, an **IL-1 antagonist**, such as the inventive compounds, would be effective to treat inflammatory bowel disease.

DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

DETD . . . antitumor effect of a non-allylating antitumor agent, being; (18) to inhibit the production of osteoclast activating factor in response to **IL-1**, being; (19) **inhibit** degranulation in response to IgE, being; (20) enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the. . .

DETD . . . an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response (such as allograft reactions), viral infection, nephritis, **mucositis**, and various allergic responses. Allergic responses include, but are not limited to, acute allergic response and thus rhinorrhea, sinus drainage,. . .

L11 ANSWER 5 OF 36 USPATFULL

AB A method for treating a disease caused by an undesirable cell response mediated by a proliferative intracellular signaling pathway is provided wherein an effective amount of a compound is administered. The compound, resolved enantiomers, diastereomers, hydrates, salts, solvates and mixtures thereof, has the formula

CORE MOIETY--(R).sub.j

wherein j is an integer from one to three; the core moiety is xanthinyl; and R is independently selected from the group consisting of amine, hydrogen, halogen, hydroxyl, C.sub.(1-10) alkyl, C.sub.(2-10) alkenyl, 2-bromopropyl, 4-chloropentyl, cyclohexyl, cyclopentyl, 3-dimethylaminobutyl, 2-hydroxyethyl, 5-hydroxyhexyl, 3-hydroxy-n-butyl, 3-hydroxypropyl, 2-methoxyethyl, 4-methoxy-n-butyl, phenyl, and formula I, at least one R comprising formula I ##STR1## wherein (CH.sub.2).sub.n is optionally substituted; n is an integer from five to twenty; each R.sub.1 or R.sub.2 is independently hydrogen or an optionally substituted group that is herein defined; and

wherein, when the (CH.sub.2).sub.n, R.sub.1 or R.sub.2 is substituted, a substituent is selected from the group consisting of carbamoyl, primary, secondary and tertiary amino, C.sub.(2-8) alkenyl, C.sub.(1-8) alkyl, C.sub.(1-8) alkoxyl, C.sub.(1-8) hydroxyalkyl, azido, carbonato, carbonyl, carboxyl, cyano, C.sub.(1-8) haloalkyl, isocyano, isomercaptocyano, phospho, phosphonato, sulfonato, alkylsulfonyl, alkylsulfoxidyl, mercaptocarbonyl, mercaptocarbonato, thioureido and ureido.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1998:111941 USPATFULL
TITLE:	Amine substituted xanthinyl compounds
INVENTOR(S):	Klein, J. Peter, Vashon, WA, United States Underiner, Gail E., Brier, WA, United States Kumar, Anil M., Seattle, WA, United States Ridgers, Lance H., Bothell, WA, United States Rice, Glenn C., Seattle, WA, United States Leung, David W., Mercer Island, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5807861		19980915	<--
APPLICATION INFO.:	US 1995-476911		19950607 (8)	
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1994-217051, filed on 24 Mar 1994, now abandoned			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Spivack, Phyllis G.			
LEGAL REPRESENTATIVE:	McDermott, Will & Emery			
NUMBER OF CLAIMS:	21			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	23 Drawing Figure(s); 23 Drawing Page(s)			
LINE COUNT:	1713			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5807861 19980915 <--

SUMM . . . not limited to acute toxicity due to effects on rapid-proliferating tissues, such as bone marrow and oral epithelium, myelosuppression and **mucositis**, renal failure and neurological, hepatic or pulmonary toxicity. Thus, for example, a cancer therapy which effectively prevented, reduced or eliminated. . .

DETD . . . mesangial cell proliferation; (2) suppress up-regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells; (3) **inhibit** TNF-, LPS- and **IL-1**-induced metalloproteases (an inflammation model); (4) block LPS-, TNF- or IL-1-induced metalloprotease and secondary cytokine production (modeling prevention or treatment of. . .

DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by. . .

DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A review article described the role of IL-1 as "an important rapid and direct determinant of disease. In septic

shock,. . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above- mentioned diseases.

DETD . . . molecules that have a role in homeostasis. The present inventive compounds address this need, identified by Dinarello et al., by **inhibiting** cellular signaling only through the **IL -1** Type I receptor and not through the IL-1 Type II receptor.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . correlate to severity of disease in patients with ulcerative colitis. Patients with inflammatory bowel disease have high tissue concentrations of IL-**1** and **IL**-8. Therefore, an **IL-1 antagonist**, such as the inventive compounds, are effective to treat inflammatory bowel disease.

DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds are useful in preventing and treating atherosclerosis.

DETD . . . enhance the antitumor effect of a non-alkylating antitumor agent; (18) to inhibit production of osteoclast activating factor in response to **IL-1**; (19) **inhibit** degranulation in response to IgE; (20) enhance release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter, acetylcholine;. . .

L11 ANSWER 6 OF 36 USPATFULL

AB Compounds and pharmaceutical compositions, including resolved enantiomers and/or diastereomers, hydrates, salts, solvates and mixtures thereof, have the formula:

CORE MOIETY --(R).sub.j

In these compounds, j is an integer from one to three; the core moiety is a cyclic core, the cyclic core being non-cyclic or at least one five- to seven-member non-heterocyclic ring or heterocycle; and R is selected from the group consisting of amine, hydrogen, halogen, hydroxyl, substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(2-10) alkenyl, cyclic or heterocyclic group or formula I. At least one R having formula I: ##STR1## In formula I, n is an integer from four to twenty; and each R.sub.1 or R.sub.2 is independently hydrogen, substituted or unsubstituted C.sub.(1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl or cyclic or heterocyclic group. The compounds are useful in treating or preventing, for example, sepsis syndrome, hematopoietic or organ toxicity, cancer, viral activity, AIDS and AIDS-related indications, allopecia caused by cytotoxic therapies, and progression of an inflammatory or autoimmune disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 1998:104752 USPATFULL

TITLE: Amine substituted compounds

INVENTOR(S): Klein, J. Peter, Vashon, WA, United States
Underiner, Gail E., Brier, WA, United States

Kumar, Anil M., Seattle, WA, United States
Ridgers, Lance H., Bothell, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5801182		19980901	<--
APPLICATION INFO.:	US 1995-485777		19950607 (8)	

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-217051, filed on 24 Mar 1994, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shah, Mukund J.
ASSISTANT EXAMINER: Coleman, Brenda
LEGAL REPRESENTATIVE: McDermott, Will & Emery
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 23 Drawing Figure(s); 23 Drawing Page(s)
LINE COUNT: 1706
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5801182 19980901 <--

SUMM . . . not limited to acute toxicity due to effects on rapid-proliferating tissues, such as bone marrow and oral epithelium, myelosuppression and **mucositis**, renal failure and neurological, hepatic or pulmonary toxicity. Thus, for example, a cancer therapy which effectively prevented, reduced or eliminated. . .

DETD . . . mesangial cell proliferation; (2) suppress upregulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells; (3) **inhibit** TNF-, LPS- and **IL-1**-induced metalloproteases (an inflammation model); (4) block LPS-, TNF- or IL-1-induced metalloprotease and secondary cytokine production (modeling prevention or treatment of. . .

DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by. . .

DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A review article described the role of IL-1 as "an important rapid and direct determinant of disease. In septic shock,. . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.

DETD . . . molecules that have a role in homeostasis. The present inventive compounds address this need, identified by Dinarello et al., by **inhibiting** cellular signaling only through the **IL-1** Type I receptor and not through the IL-1 Type II receptor.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . correlate to severity of disease in patients with ulcerative colitis. Patients with inflammatory bowel disease have high tissue concentrations of IL-**1** and **IL**-8. Therefore, an **IL-1 antagonist**, such as the inventive compounds, are effective to treat inflammatory bowel disease.

DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds are useful in preventing and treating atherosclerosis.

DETD . . . enhance the antitumor effect of a non-alkylating antitumor agent; (18) to inhibit production of osteoclast activating factor in response to **IL-1**; (19) **inhibit** degranulation in response to IgE; (20) enhance release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter, acetylcholine;. . .

L11 ANSWER 7 OF 36 USPATFULL

AB Therapeutic compounds have the formula:

(X)j--(core moiety),

J being an integer from one to three, the core moiety having at least one, five- to seven-membered ring and X being a racemic mixture, R or S enantiomer, slovate, hydrate, or salt of: ##STR1## *C is a chiral carbon atom, n is an integer from one to four (preferably from one to three), one or more carbon atoms of (CH.sub.2).sub.n may be substituted by a keto or hydroxy group, and m is an integer from one to fourteen. Independently, R.sub.1 and R.sub.2 may be a hydrogen, a straight or branched chain alkane or alkene of up to twelve carbon atoms in length, or --(CH.sub.2).sub.w R.sub.5, w being an integer from two to fourteen and R.sub.5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R.sub.5 being hydroxy, chloro, fluoro, bromo, or C.sub.1-6 alkoxy. Or jointly, R.sub.1 and R.sub.2 form a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms, N being a hetero atom. R.sub.3 is a hydrogen or C.sub.1-3. Or, therapeutic compounds may also have the formula: ##STR2## R.sub.4 is a hydrogen, a straight or branched chain alkane or alkene of up to eight carbon atoms in length, --(CH.sub.2).sub.w R.sub.5, w being an integer from two to fourteen and R.sub.5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R.sub.5 being hydroxy, chloro, fluoro, bromo, or C.sub.1-6 alkoxy, or a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms, N being a hetero atom. r and s are independently integers from one to four, the sum (r+s) not being greater than five. t is an integer from one to fourteen and one or more carbon atoms of (CH.sub.2).sub.s or (CH.sub.2).sub.t may be substituted by a keto or hydroxy group.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1998:104751 USPATFULL
TITLE:	Amino alcohol substituted cyclic compounds
INVENTOR(S):	Michnick, John, Seattle, WA, United States Underiner, Gail E., Brier, WA, United States Klein, J. Peter, Vashon Island, WA, United States Rice, Glenn C., Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5801181		19980901	<--
APPLICATION INFO.:	US 1995-474820		19950607 (8)	
RELATED APPLN. INFO.:	Division of Ser. No. US 1993-152650, filed on 12 Nov 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-40820, filed on 31 Mar 1993			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Dees, Jose G.			
ASSISTANT EXAMINER:	Pryor, Alton			
LEGAL REPRESENTATIVE:	McDermott Will & Emery			
NUMBER OF CLAIMS:	45			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	41 Drawing Figure(s); 38 Drawing Page(s)			
LINE COUNT:	2822			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5801181 19980901 <--

DRWD . . . reports inhibitive activity results for inventive compounds nos. 27, 28, 32, 30, 31, 32 and 34 in an assay measuring **inhibitive** effects in a PDGF/**IL-1** co-stimulation.

DETD . . . kidney mesengial cells; (2) suppress up-regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells; (3) **inhibit** TNF, LPS and **IL-1** induced metalloproteases (an inflammation model); (4) block LPS, TNF or IL-1 induced metalloprotease and secondary cytokine production (for prevention and. . .

DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by. . .

DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A recent review article entitled "The Role of Interleukin-1 in Disease" (Dinarello et al., N. Engl. J. Med. (1993) 106:328). . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.

DETD . . . molecules that have a role in homeostasis. The present inventive compounds address the need identified by Dinarello and Wolff by **inhibiting** cellular signaling only through the **IL-1** Type I receptor and not through the IL-1 Type II receptor.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . with ulcerative colitis, and tissue concentrations of IL-1 and IL-8 are high in patients with inflammatory bowel disease. Therefore, an **IL-1 antagonist**, such as the inventive compounds, would be effective to treat inflammatory bowel disease.

DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1

plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

DETD . . . the antitumor effect of a nonalkylating antitumor agent; (18) to inhibit the production of osteoclast activating factor in response to **IL-1**; (19) **inhibit** degranulation in response to IgE; (20) enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter,. . .

DETD . . . an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response (such as allograft reactions), viral infection, nephritis, **mucositis**, and various allergic responses. Allergic responses include acute allergic response and thus rhinorrhea, sinus drainage, diffuse tissue edema, and generalized. . .

DETD In an assay measuring **inhibitive** effects in a PDGF/**IL-1** co-stimulation, proliferation assay, a group of inventive compounds showed **inhibitive** properties. The PDGF/**IL-1** assay is useful in measuring in vitro activity, indicative of therapeutic potential for treating or preventing restenosis and reperfusion. FIG.. . .

L11 ANSWER 8 OF 36 USPATFULL

AB There is disclosed a pharmaceutical composition comprising 1-(5-oxohexyl)-3-methylxanthine in admixture with a pharmaceutically acceptable excipient, wherein the pharmaceutical composition is useful for treating an immune disorder. There is also disclosed a method to modulate the response of a target cell to a stimulus, which method comprises contacting said cell with an amount of 1-(5-oxohexyl)-3-methylxanthine or a pharmaceutical composition thereof, wherein said amount effects a diminution in elevated levels of unsaturated, non-arachidonate phosphatidic acid (PA) and diacylglycerol (DAG) derived from said PA in said cells wherein said elevated levels are stimulated by an agent capable of elevating levels of said PA and said DAG, said diminution being equal to or greater than the diminution effected by treating said cells with pentoxifylline (PTX) at a concentration of 0.5 mmol, thereby modulating the response of said target cell.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1998:98921 USPATFULL			
TITLE:	Oxohexyl methylxanthine compounds			
INVENTOR(S):	Underiner, Gail, Brier, WA, United States			
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5795897		19980818	<--
APPLICATION INFO.:	US 1994-227295		19940413 (8)	
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1992-977993, filed on 18 Nov 1992			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	MacMillan, Keith			
LEGAL REPRESENTATIVE:	Faciszewski, Stephen, Shumate, Cynthia L.			
NUMBER OF CLAIMS:	5			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 5 Drawing Page(s)			

LINE COUNT: 592
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5795897 19980818 <--
SUMM . . . of metalloproteases in synovial cells, other fibroblasts and a glomerular epithelial cell in response to inflammatory stimuli, such as TNF, **IL-1** and the like, to **inhibit** production of osteoclast-activating factor (OAP) by osteoclasts in response to **IL-1**; to **inhibit** degranulation of mast cells and basophils in response to IgE; to modulate signal transduction of the neurotransmitters epinephrine and acetylcholine. . .
DETD . . . tumor burden, a hormone-related disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

L11 ANSWER 9 OF 36 USPATFULL
AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 1998:95545 USPATFULL
TITLE: Enatiomerically pure hydroxylated xanthine compounds
INVENTOR(S): Bianco, James A., Seattle, WA, United States
Woodson, Paul, Bothell, WA, United States
Porubek, David, Edmonds, WA, United States
Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5792772		19980811	<--
APPLICATION INFO.:	US 1995-458957		19950601 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994, now patented, Pat. No. US 5652243 which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994, now patented, Pat. No. US 5648357 which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1734

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5792772 19980811 <--

DRWD . . . interleukin-2 (IL-2). CT1501R was added to the cells at the doses indicated two hours prior to activation with ConA and **IL-1**.alpha. or **IL**-2. CT1501R **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 3. Background counts were less than 200 cpm.

DRWD . . . factor) and IL-1. CT1501R and PTX were separately added to the cells two hours prior to activation with PDGF and **IL-1**. Both drugs **inhibited** smooth muscle cell proliferation at the higher doses tested as shown in FIG. 4. CT1501R was more active than PTX.

DRWD FIG. 19 shows **inhibition** of **IL-1**-.alpha. release in LPS activated PEC by CT1501R. Cells were isolated and treated with or without 250 .mu.M CT1501R one hour. . .

DRWD FIG. 20 shows **inhibition** of TNF-.alpha. release from **IL-1**-.alpha.-activated mouse peritoneal macrophages. Cells were isolated and treated with or without CT1501R (250 .mu.M) 1 hour prior to IL-1-.alpha. activation.. . .

DETD . . . up regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells of CD18 in neutrophils; (3) **inhibiting** TNF and **IL-1** induced metalloproteases (an inflammation model); (4) block LPS-induced cellular activation (for prevention and treatment of septic shock); (5) suppress T. . .

DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, CT1501R reduced PUMP-1 activity induced by 100 U/ml of. . .

DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A recent review article entitled "The Role of Interleukin- 1 in Disease" (Dinarello and Wolff N. Engl. J. Med. 328,. . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secgndaly to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.

DETD . . . of molecules that have a role in homeostasis." The present inventive compounds address the need identified by Dr. Denarello by **inhibiting** cellular signaling only through the **IL-1** Type I receptor and not through the IL-1 Type II receptor.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . with ulcerative colitis, and tissue concentrations of IL-1 and IL-8 are high in patients with inflammatory bowel disease. Therefore, an **IL-1 antagonist**, such as the inventive compounds, would be effective to treat inflammatory bowel disease.

DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

DETD . . . interleukin-2 (IL-2). CT1501R was added to the cells at the doses indicated two hours prior to activation with ConA and **IL**-1.alpha. or **IL**-2. CT1501R **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 3. Background counts were less than 200 cpm.

DETD . . . factor) and IL1. CT1501R and PTX were separately added to the cells two hours prior to activation with PDGF and **IL-1**. Both drugs **inhibited** smooth muscle cell proliferation at the higher doses tested as shown in FIG. 4 with CT1501R being more active than. . .

DETD CT1501R **inhibited** LPS, TNF-.alpha. and **IL-1**.alpha.-mediated inflammatory signaling pathways and concomitant cellular responses in peritoneal macrophages, the human U937 histiocytic leukemia cell line, and in human. . . LPS. The IC50 for TNF-.alpha. inhibition using 10 .mu.g/ml LPS stimulation was approximately 30 .mu.M. CT1501R blocked TNF-.alpha. release from **IL-1**.alpha. activated PEC. CT1501R **inhibited** the increase in adhesion of U937 cells to TNF-.alpha., IL-1.alpha. or LPS activated HUVEC. Finally, CT1501R **inhibited** **IL-1**.alpha.-induced activation and increased adhesiveness of U937 cells to non-stimulated HUVEC.

L11 ANSWER 10 OF 36 USPATFULL

AB The present invention relates to novel peptides that are potent cytokine restraining agents. In addition, the present invention relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a cytokine restraining agent. Administration of such a cytokine restraining agent to a subject restrains, but does not necessarily suppress, cytokine activity completely. Thus, the present invention provides a method of restraining pathologically elevated cytokine activity in a subject. The invention also provides methods of treating disuse deconditioning and diseases mediated by nitric oxide and cytokines, such as diabetes and glomerulonephritis, a method of organ protection, a method of organ protection, and a method of reducing the negative side effects of cancer chemotherapy, such as nephrotoxicity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1998:88817 USPATFULL
TITLE:	Cytokine restraining agents and methods of use in pathologies and conditions associated with altered cytokine levels
INVENTOR(S):	Girten, Beverly E., San Diego, CA, United States Houghten, Richard A., Del Mar, CA, United States Loullis, Costas C., Cardiff, CA, United States Suto, Mark J., San Diego, CA, United States Tuttle, Ronald R., Escondido, CA, United States
PATENT ASSIGNEE(S):	Trega Biosciences, Inc., San Diego, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5786332		19980728	<--

APPLICATION INFO.: US 1995-400983 19950306 (8)
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Tsang, Cecilia J.
ASSISTANT EXAMINER: Delacroix-Muirheid, C.
LEGAL REPRESENTATIVE: Campbell & Flores LLP
NUMBER OF CLAIMS: 46
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 1606
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5786332 19980728 <--
DETD . . . subject undergoing cancer chemotherapy to reduce other negative side effects of chemotherapeutic drugs, including but not limited to, nausea, vomiting, **mucositis**, anorexia, fatigue, and organ dysfunction.
DETD As shown in Table I, treatment with 500 .mu.g/kg EX-2 **inhibited** **IL-1**-induced fever by 52%. In addition, treatment with 50 or 150 .mu.g/kg EX-2 inhibited LPS-induced fever by 45% or 52%, respectively,. . .

L11 ANSWER 11 OF 36 USPATFULL
AB Disclosed is a process for preparing compounds having a straight or branched aliphatic hydrocarbon structure of formula I: ##STR1## In formula I, n is an integer from one to four and m is an integer from four to twenty. Independently, R.sub.1 and R.sub.2 are hydrogen, a straight or branched chain alkyl, alkenyl or alkynyl of up to twenty carbon atoms in length or --(CH.sub.2).sub.w R.sub.5. If R.sub.1 or R.sub.2 is --(CH.sub.2).sub.w R.sub.5, w may be an integer from one to twenty and R.sub.5 may be an hydroxyl, halo, C.sub.1-8 alkoxyl group or a substituted or unsubstituted carbocycle or heterocycle. Alternatively, R.sub.1 and R.sub.2 may jointly form a substituted or unsubstituted, saturated or unsaturated heterocycle having from four to eight carbon atoms, N being a hetero atom of the resulting heterocyle. R.sub.3 may be either hydrogen or C.sub.1-3. In the compounds, a total sum of carbon atoms comprising R.sub.1 or R.sub.2, (CH.sub.2).sub.n and (CH.sub.2).sub.m does not exceed forty. R.sub.4 is a terminal moiety comprising a substituted or unsubstituted, oxidized or reduced ring system, the ring system having a single ring or two to three fused rings, a ring comprising from three to seven ring atoms. The disclosed compounds are effective agents to inhibit undesirable responses to cell stimuli.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 1998:79344 USPATFULL
TITLE: Method for preparing substituted amino alcohol compounds
INVENTOR(S): Klein, J. Peter, Vashon, WA, United States
Underiner, Gail E., Brier, WA, United States
Kumar, Anil M., Seattle, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5777117		19980707	<--
APPLICATION INFO.:	US 1995-472569		19950607 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1994-303842, filed on 8 Sep

1994 which is a continuation-in-part of Ser. No. US 1993-152650, filed on 12 Nov 1993 And Ser. No. US 1993-164081, filed on 8 Dec 1993 which is a continuation-in-part of Ser. No. US 1993-40820, filed on 31 Mar 1993, now abandoned , said Ser. No. US -152650 which is a continuation-in-part of Ser. No. US -40820

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Dees, Jose G.
ASSISTANT EXAMINER: Cebulak, Mary C.
LEGAL REPRESENTATIVE: McDermott, Will & Emery
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 118 Drawing Figure(s); 92 Drawing Page(s)
LINE COUNT: 3153
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5777117 19980707 <--

SUMM . . . not limited to acute toxicity due to effects on rapid-proliferating tissues, such as bone marrow and oral epithelium, myelosuppression and **mucositis**, renal failure and neurological, hepatic or pulmonary toxicity. Thus, for example, a cancer therapy which effectively prevented, reduced or eliminated. . .

DRWD . . . 14 reports inhibitive activity results for compounds nos. 27, 28, 29, 30, 31, 32 and 34 in an assay measuring **inhibitive** effects in a PDGF/**IL-1**.beta. co-stimulation.

DETD . . . kidney mesangial cells; (2) suppress up-regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells; (3) **inhibit** TNF.alpha., LPS and **IL-1**.beta. induced metalloproteases (an inflammation and cancer metasteses model); (4) block LPS, TNF.alpha. or IL-1.beta. induced secondary cytokine production (for prevention. . .

DETD . . . IV collagenase that is usually constitutively produced and stimulated by TNF.alpha. or IL-1.beta. and a stromelysin/PUMP-1 induced by TNF.alpha. and **IL-1**.beta.. The inventive compounds can **inhibit** TNF.alpha. or **IL-1** .beta. induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by. . .

DETD The inventive compounds **inhibit IL-1** signal transduction, and are therefore considered as **IL-1 antagonists**. A review article entitled "Mechanisms of Disease: The Role of Interleukin-1 in Disease" (Dinarello et al., N. Engl. J. Med.,. . . disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.

DETD . . . of molecules that have a role in homeostasis. The present inventive compounds address the need identified by Dinarello et al. **inhibiting IL-1** cellular signaling.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . with ulcerative colitis, and tissue concentrations of IL-1.beta. and IL-8 are high in patients with inflammatory bowel

disease. Therefore, an **IL-1 antagonist**, such as the inventive compounds, is effective to treat inflammatory bowel disease.

DETD . . . IL-1.beta. also stimulates production of PDGF. Taken together, IL-1.beta. plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1**.beta. **antagonist**, such as the inventive compounds is useful in preventing and treating atherosclerosis.

DETD . . . the antitumor effect of a non-alkylating antitumor agent; (15) to inhibit the production of osteoclast activating factor in response to **IL-1**.beta.; (16) **inhibit** degranulation in response to IgE; (17) enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter,. . .

DETD In an assay measuring **inhibitive** effects in a PDGF/**IL-1**.beta. co-stimulation, proliferation assay, a group of compounds showed **inhibitive** properties. The PDGF/**IL-1**.beta. assay is useful in measuring in vitro activity, indicative of therapeutic potential for treating or preventing restenosis and reperfusion. FIG.. . .

DETD . . . amount of fluorescence remaining analyzed on a fluorescence plate reader. The results, reported in FIGS. 62A and 62B (TNF.alpha. or **IL-1**.beta., respectively), show **inhibition** of THP-1 adhesion to HUVEC.

DETD This example illustrates an ability of the compounds to **inhibit** both **IL-1**.alpha. or **IL**-6-stimulated proliferation of D10(N4)M or B9 cells, respectively. Using procedures similar to those discussed in the foregoing examples, cultures of D10(N4)M. . .

L11 ANSWER 12 OF 36 USPATFULL

AB Acetal-and ketal-substituted compounds and pharmaceutical compositions thereof have the following formula:

CORE MOIETY--(R).sub.j,

including resolved enantiomers and/or diastereomers, hydrates, salts, solvates and mixtures thereof. j is an integer from one to three, the core moiety is non-cyclic or cyclic a monocyclic moiety having at least one nitrogen atom within the ring and R may be selected from among hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted alkyl C.sub.(1-6), alkenyl C.sub.(2-6), cyclic or heterocyclic groups, and groups having a structure prescribed by formula I. At least one R has the formula I:

--(CH.sub.2).sub.n --C--(R.sub.1).sub.3 I

wherein n is an integer from three to twenty; R.sub.1 is selected from among hydrogen; halogen; hydroxide; substituted or unsubstituted C.sub.(1-6) alkyl, C.sub.(1-6) alkoxy, C.sub.2-6) alkenyl, cyclic or heterocyclic group; --OR.sub.2, R.sub.2 being hydrogen or a substituted or unsubstituted C.sub.(1-6) alkyl, C.sub.(2-6) alkenyl, cyclic or heterocyclic group; --(CH.sub.2).sub.p --C(R.sub.3).sub.3 (wherein p is zero or an integer from one to ten, R.sub.3 is hydrogen, halogen, hydroxide, substituted or unsubstituted C.sub.(1-6) alkyl, C.sub.(1-6) alkoxy, C.sub.(2-6) alkenyl, cyclic or heterocyclic group, or --OR.sub.2, R.sub.2 being defined above). The inventive compounds are useful in a large variety of therapeutic indications for treating or

preventing disease mediated by intracellular signaling through specific intracellular signaling pathways.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1998:79342 USPATFULL
TITLE:	Acetal-and ketal-substituted pyrimidine compounds
INVENTOR(S):	Leigh, Alistair, Brier, WA, United States Underiner, Gail, Brier, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5777115		19980707	<--
APPLICATION INFO.:	US 1994-193331		19940207 (8)	

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1993-4353, filed on 14 Jan 1993, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Shah, Mukund J.
ASSISTANT EXAMINER:	Sripada, Pavanaram K.
LEGAL REPRESENTATIVE:	Foley & Lardner
NUMBER OF CLAIMS:	13
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	9 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT:	1632

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5777115 19980707 <--

DETD . . . kidney mesengial cells; (2) suppress up-regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells; (3) **inhibit** TNF, LPS and **IL-1** induced metalloproteases (an inflammation model); (4) block LPS, TNF or IL-1 induced metalloprotease and secondary cytokine production (for prevention and. . .

DETD . . . IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP- 1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by. . .

DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A recent review article entitled "The Role of Interleukin-1 in Disease" (Dinarello et al., N. Engl. J. Med. 328, 106,. . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.

DETD . . . molecules that have a role in homeostasis. The present inventive compounds address this need, identified by Dinarello et al., by **inhibiting** cellular signaling only through the **IL-1** Type I receptor and not through the IL-1 Type II receptor.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid

arthritis.

DETD . . . correlate to severity of disease in patients with ulcerative colitis, patients with inflammatory bowel disease having high tissue concentrations of IL-**1** and **IL**-8. Therefore, an **IL-1 antagonist**, such as the inventive compounds, would be effective to treat inflammatory bowel disease.

DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

DETD . . . tumor burden, a hormone-related disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis** , and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

DETD . . . in a liquid scintillation counter. Drug was added at the doses indicated two hours prior to activation with ConA and **IL**-**1**.alpha.. Compound no. 1567 **inhibited** thymocyte proliferation in a dose-response manner as shown in FIG. 2. Background counts were less than 200 cpm.

L11 ANSWER 13 OF 36 USPATFULL

AB Oxime-substituted compounds are preferably cyclic or heterocyclic compounds. The oxime-substituted compounds and pharmaceutical compositions thereof have the formula:

CORE MOIETY--(R).sub.j

including resolved enantiomers (both syn and anti forms) and/or diastereomers, hydrates, salts, solvates and mixtures thereof. j is an integer from one to three, the core moiety is non-cyclic or cyclic and R may be selected from among: hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted C.sub.(1-10), alkyl, C.sub.(2-10) alkenyl, cyclic or heterocyclic groups, and formula I. At least one R has the formula I:

--(CH.sub.2).sub.n --C--(R.sub.1).sub.p, I

wherein n is an integer from three to twenty; p is two or three; R.sub.1 is selected from among hydrogen; halogen; hydroxide; substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(1-10) alkoxy, C.sub.(2-10) alkenyl, cyclic or heterocyclic group; =N--OR.sub.2, R.sub.2 being hydrogen or a substitute or unsubstituted C.sub.(1-10) alkyl, C.sub.(2-10) alkenyl, cyclic or heterocyclic group; and --(CH.sub.2).sub.s --C(R.sub.3).sub.t (wherein s is zero or an integer from one to ten, t is two or three, R.sub.3 is hydrogen, halogen, hydroxide, substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(1-10) alkoxy, C(.sub.2-10) alkenyl, cyclic or heterocyclic group, or .dbd.N--OR.sub.2, R.sub.2 being defined above). At least one R.sub.1 or one R.sub.3 is .dbd.N--OR.sub.2, p or t corresponding to the at least one R.sub.1 or one R.sub.3 is two, and a second R.sub.1 or second R.sub.3, bonded to the same --C as the at least one R.sub.1 or one R.sub.3, is other than .dbd.N--OR.sub.2. These disclosed compounds are useful in a large variety of therapeutic indications for treating or preventing disease mediated by intracellular signaling through specific intracellular signaling pathways.

ACCESSION NUMBER: 1998:72620 USPATFULL
TITLE: Oxime substituted therapeutic compounds
INVENTOR(S): Klein, J. Peter, Vashon, WA, United States
Leigh, Alistair, Brier, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5770595		19980623	<--
APPLICATION INFO.:	US 1994-193344		19940207 (8)	

RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-6083, filed on 19 Jan 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: MacMillan, Keith
LEGAL REPRESENTATIVE: Faciszewski, Stephen
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 19 Drawing Figure(s); 19 Drawing Page(s)
LINE COUNT: 2183
PI US 5770595 19980623 <--
DRWD FIG. 5 illustrates the ability of inventive compound no. 1521 to **inhibit IL-1**.alpha. release from murine peritoneal macrophages when stimulated with LPS. This assay is a model for septic shock. As represented in FIG. 5, 1521 **inhibited IL-1**.alpha. release.
DRWD FIG. 8 reports data illustrating the ability of inventive compound no. 1521 to **inhibit IL-1**.alpha. release from P388D1 cells when stimulated with LPS. This assay is a model for septic shock. The data in FIG. 8 show **inhibition** of **IL-1**.alpha. release by compound no. 1521.
DRWD FIG. 14 reports data obtained in an assay measuring an ability of inventive compound no. 2525 to **inhibit** THP-1 cell adhesion to **IL-1**.beta.-activated HUVEC.
DETD . . . kidney mesengial cells; (2) suppress up-regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells; (3) **inhibit** TNF, LPS and **IL-1** induced metalloproteases (an inflammation model); (4) block LPS, TNF or IL-1 induced metalloprotease and secondary cytokine production (for prevention and. . .
DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by. . .
DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A recent review article entitled "The Role of Interleukin-1 in Disease" (Dinarello et al., N. Engl. J. Med. 328, 106,. . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.
DETD . . . molecules that have a role in homeostasis. The present

inventive compounds address this need, identified by Dinarello et al., by **inhibiting** cellular signaling only through the **IL-1** Type I receptor and not through the IL-1 Type II receptor.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . correlate to severity of disease in patients with ulcerative colitis, patients with inflammatory bowel disease having high tissue concentrations of IL-**1** and **IL**-8. Therefore, an **IL-1 antagonist**, such as the inventive compounds, would be effective to treat inflammatory bowel disease.

DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

DETD . . . tumor burden, a hormone-related disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

DETD . . . in a liquid scintillation counter. Drug was added at the doses indicated two hours prior to activation with ConA an **IL-1**.alpha.. Compound no. 1521 **inhibited** thymocyte proliferation in a dose-response manner a is shown in FIG. 2. Background counts were less than 200 cpm.

DETD . . . Compound no 1522 was added to the cells at the doses indicated two hours prior to activation with ConA and **IL-1**.alpha.. Compound no. 1522 **inhibited** thymocyte proliferation as is shown in FIG. 3. Background counts were less than 200 cpm.

DETD This example illustrates the ability of inventive compound no. 1521 to **inhibit IL-1**.alpha. release from murine peritoneal macrophages when stimulated with LPS. This assay is a model for septic shock. Macrophages (10.sup.5) were. . . LPS stimulation with 0.25 mM 1521. As can be seen from the data reported in FIG. 5, compound no. 1521 **inhibited IL-1**.alpha. release.

DETD This example illustrates the ability of inventive compound no. 1521 to **inhibit IL-1**.alpha. release from P388D1 cells when stimulated with LPS. This assay is a model for septic shock. P388D1 cells (10.sup.5) were. . . with 0.25 mM of compound no. 1521. As can be deduced from data reported in FIG. 8, compound no. 1521 **inhibited IL-1**.alpha. release.

L11 ANSWER 14 OF 36 USPATFULL

AB The present invention relates to novel peptides that are potent cytokine restraining agents. In addition, the present invention relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a cytokine restraining agent. Administration of such a cytokine restraining agent to a subject restrains, but does not necessarily suppress, cytokine activity completely. Thus, the present invention provides a method of restraining pathologically elevated cytokine activity in a subject. The invention also provides methods of treating disuse deconditioning and diseases mediated by nitric oxide and cytokines, such as diabetes and glomerulonephritis, a method of organ protection, a method of organ protection, and a method of reducing the

negative side effects of cancer chemotherapy, such as nephrotoxicity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1998:61616 USPATFULL
TITLE:	Cytokine restraining agents and methods of use in pathologies and conditions associated with altered cytokine levels
INVENTOR(S):	Girten, Beverly E., San Diego, CA, United States Houghten, Richard A., Del Mar, CA, United States Loullis, Costas C., Cardiff, CA, United States Suto, Mark J., San Deigo, CA, United States Tuttle, Ronald R., Escondido, CA, United States
PATENT ASSIGNEE(S):	Trega Biosciences, Inc., San Diego, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5760001		19980602	<--
APPLICATION INFO.:	US 1995-447143		19950522 (8)	
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1995-400983, filed on 6 Mar 1995			

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Tsang, Cecilia J.
ASSISTANT EXAMINER:	Delacroix-Muirheid, C.
LEGAL REPRESENTATIVE:	Campbell & Flores LLP
NUMBER OF CLAIMS:	22
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT:	1474

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5760001 19980602 <--

DETD . . . subject undergoing cancer chemotherapy to reduce other negative side effects of chemotherapeutic drugs, including but not limited to, nausea, vomiting, **mucositis**, anorexia, fatigue, and organ dysfunction.

DETD As shown in Table I, treatment with 500 .mu.g/kg EX-2 **inhibited IL-1**-induced fever by 52%. In addition, treatment with 50 or 150 .mu.g/kg EX-2 inhibited LPS-induced fever by 45% or 52%, respectively,. . .

L11 ANSWER 15 OF 36 USPATFULL

AB Disclosed are compounds having a straight or branched aliphatic hydrocarbon structure of formula I: ##STR1## In formula I, n is an integer from one to four and m is an integer from four to twenty. Independently, R.sub.1 and R.sub.2 are hydrogen, a straight or branched chain alkyl, alkenyl or alkynyl of up to twenty carbon atoms in length or --(CH.sub.2).sub.w R.sub.5. If R.sub.1 or R.sub.2 is --(CH.sub.2).sub.w R.sub.5, w may be an integer from one to twenty and R.sub.5 may be an hydroxyl, halo, C.sub.1-8 alkoxyl group or a substituted or unsubstituted carbocycle or heterocycle. Alternatively, R.sub.1 and R.sub.2 may jointly form a substituted or unsubstituted, saturated or unsaturated heterocycle having from four to eight carbon atoms, N being a hetero atom of the resulting heterocyle. R.sub.3 may be either hydrogen or C.sub.1-3. In the compounds, a total sum of carbon atoms comprising R.sub.1 or R.sub.2, (CH.sub.2).sub.n and (CH.sub.2).sub.m does not exceed forty. R.sub.4 is a carbocycle comprising a substituted or unsubstituted ring system, the ring system

having a single ring or two fused rings, a ring comprising from three to seven ring atoms. The disclosed compounds are effective agents to inhibit undesirable responses to cell stimuli.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1998:51651 USPATFULL
TITLE:	Substituted amino alcohol compounds
INVENTOR(S):	Klein, J. Peter, Vashon, WA, United States Underiner, Gail E., Brier, WA, United States Kumar, Anil M., Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5750575		19980512	<--
APPLICATION INFO.:	US 1995-475721		19950607 (8)	
RELATED APPLN. INFO.:	Division of Ser. No. US 1994-303842, filed on 8 Sep 1994, now patented, Pat. No. US 5641783 which is a continuation-in-part of Ser. No. US 1993-152650, filed on 12 Nov 1993 And a continuation-in-part of Ser. No. US 1993-164081, filed on 8 Dec 1993, now patented, Pat. No. US 5470878 which is a continuation-in-part of Ser. No. US 1993-40820, filed on 31 Mar 1993, now abandoned			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Dees, Jose G.			
ASSISTANT EXAMINER:	Cebulak, M.			
LEGAL REPRESENTATIVE:	McDermott, Will & Emery, Faciszewski, Esq., Stephen			
NUMBER OF CLAIMS:	18			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	115 Drawing Figure(s); 90 Drawing Page(s)			
LINE COUNT:	3115			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5750575 19980512 <--

SUMM . . . not limited to acute toxicity due to effects on rapid-proliferating tissues, such as bone marrow and oral epithelium, myelosuppression and **mucositis**, renal failure and neurological, hepatic or pulmonary toxicity. Thus, for example, a cancer therapy which effectively prevented, reduced or eliminated. . .

DRWD . . . 14 reports inhibitive activity results for compounds nos. 27, 28, 29, 30, 31, 32 and 34 in an assay measuring **inhibitive** effects in a PDGF/**IL-1**.beta. co-stimulation.

DETD . . . kidney mesangial cells; (2) suppress up-regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells; (3) **inhibit** TNF.alpha., LPS and **IL-1**.beta. induced metalloproteases (an inflammation and cancer metasteses model); (4) block LPS, TNF.alpha. or IL-1.beta. induced secondary cytokine production (for prevention. . .

DETD . . . IV collagenase that is usually constitutively produced and stimulated by TNF.alpha. or IL-1.beta., and a stromelysin/PUMP-1 induced by TNF.alpha. and **IL-1**.beta.. The inventive compounds can **inhibit** TNF.alpha. or **IL-1** .beta. induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by. . .

DETD The inventive compounds **inhibit IL-1** signal transduction, and are therefore considered as **IL-**

1 antagonists. A review article entitled "Mechanisms of Disease: The Role of Interleukin-1 in Disease" (Dinarello et al., N. Engl. J. Med.,. . . disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.

DETD . . . of molecules that have a role in homeostasis. The present inventive compounds address the need identified by Dinarello et al. **inhibiting IL-1** cellular signaling.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . with ulcerative colitis, and tissue concentrations of IL-1.beta. and IL-8 are high in patients with inflammatory bowel disease. Therefore, an **IL-1 antagonist**, such as the inventive compounds, is effective to treat inflammatory bowel disease.

DETD . . . IL-1.beta. also stimulates production of PDGF. Taken together, IL-1.beta. plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1**.beta. **antagonist**, such as the inventive compounds is useful in preventing and treating atherosclerosis.

DETD . . . the antitumor effect of a non-alkylating antitumor agent; (15) to inhibit the production of osteoclast activating factor in response to **IL-1**.beta.; (16) **inhibit** degranulation in response to IgE; (17) enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter,. . .

DETD In an assay measuring **inhibitive** effects in a PDGF/**IL -1**.beta. co-stimulation, proliferation assay, a group of compounds showed **inhibitive** properties. The PDGF/**IL-1**.beta. assay is useful in measuring in vitro activity, indicative of therapeutic potential for treating or preventing restenosis and reperfusion. FIG.. . .

DETD . . . amount of fluorescence remaining analyzed on a fluorescence plate reader. The results, reported in FIGS. 62A and 62B (TNF.alpha. or **IL-1**.beta., respectively), show **inhibition** of THP-1 adhesion to HUVEC.

DETD This example illustrates an ability of the compounds to **inhibit** both **IL-1**.alpha. or **IL**-6-stimulated proliferation of D10(N4)M or B9 cells, respectively. Using procedures similar to those discussed in the foregoing examples, cultures of D10(N4)M. . .

L11 ANSWER 16 OF 36 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 1998:39529 USPATFULL

09/800,855

TITLE:	Enantiomerically pure hydroxylated xanthine compounds to treat autoimmune diabetes
INVENTOR(S):	Bianco, James A., Seattle, WA, United States Woodson, Paul, Bothell, WA, United States Porubek, David, Edmonds, WA, United States Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5739138		19980414	<--
APPLICATION INFO.:	US 1995-457703		19950601 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994, now abandoned which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994, now abandoned which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Criares, Theodore J.
LEGAL REPRESENTATIVE:	Faciszewski, Stephen
NUMBER OF CLAIMS:	2
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT:	1734

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5739138 19980414 <--

DRWD . . . interleukin-2 (IL-2). CT1501R was added to the cells at the doses indicated two hours prior to activation with ConA and **IL-1**.alpha. or **IL-2**. CT1501R **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 3. Background counts were less than 200 cpm.

DRWD . . . factor) and IL-1. CT1501R and PTX were separately added to the cells two hours prior to activation with PDGF and **IL-1**. Both drugs **inhibited** smooth muscle cell proliferation at the higher doses tested as shown in FIG. 4. CT1501R was more active than PTX.

DRWD FIG. 19 shows **inhibition** of **IL-1**-.alpha. release in LPS activated PEC by CT1501R. Cells were isolated and treated with or without 250 .mu.M CT1501R one hour. . .

DRWD FIG. 20 shows **inhibition** of TNF-.alpha. release from **IL-1**-.alpha.-activated mouse peritoneal macrophages. Cells were isolated and treated with or without CT1501R (250 .mu.M) 1 hour prior to IL-1-.alpha. activation.. . .

DETD . . . up regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells of CD18 in neutrophils; (3) **inhibiting** TNF and **IL-1** induced metalloproteases (an inflammation model); (4) block LPS-induced cellular activation (for prevention and treatment of septic shock); (5) suppress T. . .

DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase

inducable metalloprotease. Moreover, CT 1501R reduced PUMP-1 activity induced by 100 U/ml. . .

DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A recent review article entitled "The Role of Interleukin-1 in Disease" (Dinarello and Wolff N. Engl. J. Med. 328, 106,. . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.

DETD . . . of molecules that have a role in homeostasis." The present inventive compounds address the need identified by Dr. Denarello by **inhibiting** cellular signaling only through the **IL-1** Type I receptor and not through the IL-1 Type II receptor.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . with ulcerative colitis, and tissue concentrations of IL-1 and IL-8 are high in patients with inflammatory bowel disease. Therefore, an **IL-1 antagonist**, such as the inventive compounds, would be effective to treat inflammatory bowel disease.

DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

DETD . . . interleukin-2 (IL-2). CT1501R was added to the cells at the doses indicated two hours prior to activation with ConA and **IL-1**.alpha. or **IL-2**. CT1501R **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 3. Background counts were less than 200 cpm.

DETD . . . factor) and IL-1. CT1501R and PTX were separately added to the cells two hours prior to activation with PDGF and **IL-1**. Both drugs **inhibited** smooth muscle cell proliferation at the higher doses tested as shown in FIG. 4 with CT1501R being more active than. . .

DETD CT1501R **inhibited** LPS, TNF-.alpha. and **IL-1**.alpha.-mediated inflammatory signaling pathways and concomitant cellular responses in peritoneal macrophages, the human U937 histiocytic leukemia cell line, and in human. . . LPS. The IC50 for TNF-.alpha. inhibition using 10 .mu.g/ml LPS stimulation was approximately 30 .mu.M. CT1501R blocked TNF-.alpha. release from **IL-1**.alpha. activated PEC. CT1501R **inhibited** the increase in adhesion of U937 cells to TNF-.alpha., IL-1.alpha. or LPS activated HUVEC. Finally; CT1501R **inhibited IL-1**.alpha.-induced activation and increased adhesiveness of U937 cells to non-stimulated HUVEC.

L11 ANSWER 17 OF 36 USPATFULL

AB The present invention relates to novel peptides that are potent cytokine regulatory agents. In addition, the present invention relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a cytokine regulatory agent. Administration of such a cytokine regulatory agent to a subject can enhance or restrain cytokine activity. Thus, the present invention provides a method of regulating cytokine activity in a subject having a condition characterized by aberrant or altered cytokine activity. The invention also provides methods of treating such conditions, including, for example, disuse deconditioning, diseases mediated by nitric oxide and cytokines, adverse drug reactions, obesity, septic shock, and adverse side effects due to cancer chemotherapy or occurring as in response to organ transplantation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 1998:25211 USPATFULL

TITLE: Cytokine regulatory agents and methods of use in pathologies and conditions associated with altered cytokine levels

INVENTOR(S): Girten, Beverly E., San Diego, CA, United States
Andalibi, Ali, San Diego, CA, United States
Basu, Amaresh, San Diego, CA, United States
Fagan, Patrick, Escondido, CA, United States
Houghten, Richard A., Del Mar, CA, United States
Loullis, Costas C., Cardiff, CA, United States
Omholt, Paul, San Diego, CA, United States
Tuttle, Ronald R., Escondido, CA, United States
Suto, Mark J., San Diego, CA, United States
Weber, Patricia A., Stevensville, MT, United States

PATENT ASSIGNEE(S): Trega Biosciences, Inc., San Diego, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5726156		19980310	<--
APPLICATION INFO.:	US 1995-527056		19950912 (8)	

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-484262, filed on 7 Jun 1995, now abandoned which is a continuation-in-part of Ser. No. US 1995-400983, filed on 6 Mar 1995

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Tsang, Cecilia J.
ASSISTANT EXAMINER: Delacroix-Muirheid, C.
LEGAL REPRESENTATIVE: Campbell & Flores LLP
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 1873

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5726156 19980310 <--

DETD . . . subject undergoing cancer chemotherapy to reduce other negative side effects of chemotherapeutic drugs, including but not limited to, nausea, vomiting, **mucositis**, anorexia, fatigue, and other organ dysfunctions.

DETD As shown in Table I, treatment with 500 .mu.g/kg EX-2 **inhibited** **IL-1**-induced fever by 52%. In addition, treatment with 50 or 150 .mu.g/kg EX-2 inhibited LPS-induced fever by 45% or 52%,

respectively,. . .

L11 ANSWER 18 OF 36 USPATFULL

AB There is disclosed a compound having the formula: ##STR1## wherein n is an integer from 5 to 9, wherein the core moiety is a heterocylic moiety wherein C.sub.a, C.sub.b, and C.sub.c are an R or S enantiomer or racemic mixture and the C.sub.a, C.sub.b, and C.sub.c carbon atoms are bonded together by a single bond, double bond, ether or ester linkages, wherein R.sub.1, R.sub.2 and R.sub.3 are independently halo, hydroxy, hydrogen, keto, isothiocyano, azide or haloacetoxy with the proviso that at least one of R.sub.1, R.sub.2 or R.sub.3 must be a halo, isothiocyano, azide or haloacetoxy group, wherein R.sub.4 is hydrogen, C.sub.1-6 alkyl, C.sub.1-6 alkenyl, cyclo C.sub.4-6 alkyl, or phenyl, and wherein halo refers to fluoro, chloro, bromo and iodo and salts thereof and pharmaceutical compositions thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 97:86614 USPATFULL
TITLE: Halogen, isothiocyanate or azide substituted xanthines
INVENTOR(S): Leigh, Alistair, Brier, WA, United States
Michnick, John, Seattle, WA, United States
Kumar, Anil, Seattle, WA, United States
Underiner, Gail, Brier, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5670506		19970923	<--
APPLICATION INFO.:	US 1993-42946		19930405	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shah, Mukund J.
ASSISTANT EXAMINER: Sripada, Pavanaram K.
LEGAL REPRESENTATIVE: Faciszewski, Stephen
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Figure(s); 14 Drawing Page(s)
LINE COUNT: 1994

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5670506 19970923 <--

DRWD . . . 3T3 cells with IL-1.beta.. CT1595 is a potent drug to inhibit enzyme activity that generates PA and then DAG by **inhibiting** **IL-1**-induced signal transduction, through this second messenger pathway, via the Type I **IL-1** receptor. The **inhibiting** activity was not in a dose-response manner, indication that the IC50 concentration for inhibiting cellular second messenger signaling is probably. . .

DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

DETD . . . up regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells of CD18 in neutrophils; (3) **inhibiting** TNF, LPS and **IL-1** induced metalloproteases (an inflammation model); (4) block LPS, TNF or IL-1

induced cellular activation (for prevent and treatment of septic. . .

DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by. . .

DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A review article entitled "The Role of Interleukin-1 in Disease" (Dinarello and Wolff N. Engl. J. Med. 328:106, 1993) described. . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.

DETD . . . molecules that have a role in homeostasis." The present inventive compounds address the need identified by Dinarello and Wolff by **inhibiting** cellular signaling only through the **IL-1** Type I receptor and not through the IL-1 Type II receptor.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . with ulcerative colitis, and tissue concentrations of IL-1 and IL-8 are high in patients with inflammatory bowel disease. Therefore, an **IL-1 antagonist**, such as the inventive compounds, would be effective to treat inflammatory bowel disease.

DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

DETD . . . 3T3 cells with IL-1.beta.. CT1595 is a potent drug to inhibit enzyme activity that generates PA and then DAG by **inhibiting** **IL-1**-induced signal transduction, through this second messenger pathway, via the Type I **IL-1** receptor. The **inhibiting** activity was not in a dose-response manner, indicating that the IC50 concentration for inhibiting cellular second messenger signaling is probably. . .

L11 ANSWER 19 OF 36 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 97:66130 USPATFULL

TITLE: Methods of using enantiomerically pure hydroxylated xanthine compounds

INVENTOR(S): Bianco, James A., Seattle, WA, United States
Singer, Jack, Seattle, WA, United States

PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States

(U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5652243		19970729	<--
APPLICATION INFO.:	US 1994-343810		19941122 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1994-307554, filed on 16 Sep 1994 which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: Oster, Jeffrey B., Faciszewski, Stephen
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1731
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5652243 19970729 <--

DRWD . . . interleukin-2 (IL-2). CT1501R was added to the cells at the doses indicated two hours prior to activation with ConA and **IL-1**.alpha. or **IL**-2. CT1501R **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 3. Background counts were less than 200 cpm.

DRWD . . . factor) and IL-1. CT1501R and PTX were separately added to the cells two hours prior to activation with PDGF and **IL-1** . Both drugs **inhibited** smooth muscle cell proliferation at the higher doses tested as shown in FIG. 4. CT1501R was more active than PTX.

DRWD FIG. 19 shows **inhibition** of **IL-1**-.alpha. release in LPS activated PEC by CT1501R. Cells were isolated and treated with or without 250 .mu.M CT1501R one hour. . .

DRWD FIG. 20 shows **inhibition** of TNF-.alpha. release from **IL-1**-.alpha.-activated mouse peritoneal macrophages. Cells were isolated and treated with or without CT1501R (250 .mu.M) 1 hour prior to IL-1-.alpha. activation.. . .

DETD . . . up regulation of adhesion molecules as shown, for example; by blocking VCAM in endothelial cells of CD18 in neutrophils; (3) **inhibiting** TNF and **IL-1** induced metalloproteases (an inflammation model); (4) block LPS-induced cellular activation (for prevention and treatment of septic shock); (5) suppress T. . .

DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, CT1501R reduced PUMP-1 activity induced by 100 U/ml of. . .

DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A recent review article entitled "The Role of Interleukin-1 in Disease" (Dinarello and Wolff N. Engl. J. Med. 328, 106,. . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are

IL-1 antagonists, the inventive compounds are useful for treating all of the above-mentioned diseases.

DETD . . . of molecules that have a role in homeostasis." The present inventive compounds address the need identified by Dr. Denarello by **inhibiting** cellular signaling only through the **IL-1** Type I receptor and not through the IL-1 Type II receptor.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . with ulcerative colitis, and tissue concentrations of IL-1 and IL-8 are high in patients with inflammatory bowel disease. Therefore, an **IL-1 antagonist**, such as the inventive compounds, would be effective to treat inflammatory bowel disease.

DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

DETD . . . hormone-related disorder, a neurological disorder, an autoimmune disease/inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

DETD . . . interleukin-2 (IL-2). CT1501R was added to the cells at the doses indicated two hours prior to activation with ConA and **IL-1**.alpha. or **IL-2**. CT1501R **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 3. Background counts were less than 200 cpm.

DETD . . . factor) and IL-1. CT1501R and PTX were separately added to the cells two hours prior to activation with PDGF and **IL-1**. Both drugs **inhibited** smooth muscle cell proliferation at the higher doses tested as shown in FIG. 4 with CT1501R being more active than. . .

DETD CT1501R **inhibited** LPS, TNF-.alpha. and **IL-1**.alpha.-mediated inflammatory signaling pathways and concomitant cellular responses in peritoneal macrophages, the human U937 histiocytic leukemia cell line, and in human. . . LPS. The IC50 for TNF-.alpha. inhibition using 10 .mu.g/ml LPS stimulation was approximately 30 .mu.M. CT1501R blocked TNF-.alpha. release from **IL-1**.alpha. activated PEC. CT1501R **inhibited** the increase in adhesion of U937 cells to TNF-.alpha., IL-1.alpha. or LPS activated HUVEC. Finally, CT1501R **inhibited IL-1**.alpha.-induced activation and increased adhesiveness of U937 cells to non-stimulated HUVEC.

CLM What is claimed is:
4. The method of claim 1 wherein the organ toxicity is gastrointestinal **mucositis**.

L11 ANSWER 20 OF 36 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in

effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	97:61689 USPATFULL
TITLE:	Enatiomerically pure hydroxylated xanthine compounds
INVENTOR(S):	Bianco, James A., Seattle, WA, United States Woodson, Paul, Bothell, WA, United States Porubek, David, Edmonds, WA, United States Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5648357		19970715	<--
APPLICATION INFO.:	US 1994-307554		19940916 (8)	

RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Criares, Theodore J.
LEGAL REPRESENTATIVE:	Oster, Jeffrey B., Faciszewski, Stephen
NUMBER OF CLAIMS:	10
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT:	1748

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5648357 19970715 <--

DRWD . . . interleukin-2 (IL-2). CT1501R was added to the cells at the doses indicated two hours prior to activation with ConA and **IL**-**1**.alpha. or **IL**-2. CT1501R **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 3. Background counts were less than 200 cpm.

DRWD . . . factor) and IL-1. CT1501R and PTX were separately added to the cells two hours prior to activation with PDGF and **IL-1**. Both drugs **inhibited** smooth muscle cell proliferation at the higher doses tested as shown in FIG. 4. CT1501R was more active than PTX.

DRWD FIG. 19 shows **inhibition** of **IL-1**-.alpha. release in LPS activated PEC by CT1501R. Cells were isolated and treated with or without 250 .mu.M CT1501R one hour. . .

DRWD FIG. 20 shows **inhibition** of TNF-.alpha. release from **IL-1**-.alpha.-activated mouse peritoneal macrophages. Cells were isolated and treated with or without CT1501R (250 .mu.M) 1 hour prior to IL-1-.alpha. activation.. . .

DETD . . . up regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells of CD18 in neutrophils; (3) **inhibiting** TNF and **IL-1** induced metalloproteases (an inflammation model); (4) block LPS-induced cellular activation (for prevention and treatment of septic shock); (5) suppress T. . .

DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and **IL**-**1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase

inducable metalloprotease. Moreover, CT1501R reduced PUMP-1 activity induced by 100 U/ml of. . .

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DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

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DETD . . . interleukin-2 (IL-2). CT1501R was added to the cells at the doses indicated two hours prior to activation with ConA and **IL-1**.alpha. or **IL**-2. CT1501R **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 3. Background counts were less than 200 cpm.

DETD . . . factor) and IL-1. CT1501R and PTX were separately added to the cells two hours prior to activation with PDGF and **IL-1**. Both drugs **inhibited** smooth muscle cell proliferation at the higher doses tested as shown in FIG. 4 with CT1501R being more active than. . .

DETD CT1501R **inhibited** LPS, TNF-.alpha. and **IL-1**.alpha.-mediated inflammatory signaling pathways and concomitant cellular responses in peritoneal macrophages, the human U937 histiocytic leukemia cell line, and in human. . . LPS. The IC50 for TNF-.alpha. inhibition using 10 .mu.g/ml LPS stimulation was approximately 30 .mu.M. CT1501R blocked TNF-.alpha. release from **IL-1**.alpha. activated PEC. CT1501R **inhibited** the increase in adhesion of U937 cells to TNF-.alpha., IL-1.alpha. or LPS activated HUVEC. Finally, CT1501R **inhibited IL-1**.alpha.-induced activation and increased adhesiveness of U937 cells to non-stimulated HUVEC.

L11 ANSWER 21 OF 36 USPATFULL

AB Disclosed are compounds having a straight or branched aliphatic hydrocarbon structure of formula I: ##STR1## In formula I, n is an integer from one to four and m is an integer from four to twenty. Independently, R.sub.1 and R.sub.2 are hydrogen, a straight or branched chain alkyl, alkenyl or alkynyl of up to twenty carbon atoms in length or --(CH.sub.2).sub.w R.sub.5. If R.sub.1 or R.sub.2 is --(CH.sub.2).sub.w R.sub.5, w may be an integer from one to twenty and R.sub.5 may be an hydroxyl, halo, C.sub.1-8 alkoxyl group or a substituted or unsubstituted carbocycle or heterocycle. Alternatively, R.sub.1 and R.sub.2 may jointly form a substituted or unsubstituted, saturated or unsaturated heterocycle having from four to eight carbon atoms, N being a hetero atom of the resulting heterocycle. R.sub.3 may be either hydrogen or C.sub.1-3. In the compounds, a total sum of carbon atoms comprising R.sub.1 or R.sub.2, (CH.sub.2).sub.n and (CH.sub.2).sub.m does not exceed forty. R.sub.4 is a terminal moiety comprising a substituted or unsubstituted, oxidized or reduced ring system, the ring system having a single ring or two to three fused rings, a ring comprising from three to seven ring atoms. The disclosed compounds are effective agents to inhibit undesirable responses to cell stimuli.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 97:54233 USPATFULL

TITLE: Substituted amino alcohol compounds

INVENTOR(S): Klein, J. Peter, Vashon, WA, United States
Underiner, Gail E., Brier, WA, United States
Kumar, Anil M., Seattle, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5641783		19970624	<--
APPLICATION INFO.:	US 1994-303842		19940908 (8)	

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1993-152650, filed on 12 Nov 1993 And Ser. No. US 1993-164081, filed on 8 Dec 1993, now patented, Pat. No. US 5470878

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Raymond, Richard L.
ASSISTANT EXAMINER: Cebulak, Mary C.
LEGAL REPRESENTATIVE: Faciszewski, Stephen, Oster, Jeffrey B.
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 115 Drawing Figure(s); 88 Drawing Page(s)
LINE COUNT: 3206

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5641783 19970624 <--

SUMM . . . not limited to acute toxicity due to effects on rapid-proliferating tissues, such as bone marrow and oral epithelium, myelosuppression and **mucositis**, renal failure and neurological, hepatic or pulmonary toxicity. Thus, for example, a cancer therapy which effectively prevented, reduced or eliminated. . .

DRWD . . . 14 reports inhibitive activity results for compounds nos. 27, 28, 29, 30, 31, 32 and 34 in an assay measuring **inhibitive** effects in a PDGF/**IL-1**.beta. co-stimulation.

DETD . . . kidney mesangial cells; (2) suppress up-regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells;

(3) **inhibit** TNF.alpha., LPS and **IL-1**.beta. induced metalloproteases (an inflammation and cancer metasteses model); (4) block LPS, TNF.alpha. or IL-1.beta. induced secondary cytokine production (for prevention. . .

DETD . . . IV collagenase that is usually constitutively produced and stimulated by TNF.alpha. or IL-1.beta., and a stromelysin/PUMP-1 induced by TNF.alpha. and **IL-1**.beta.. The inventive compounds can **inhibit** TNF.alpha. or **IL-1** .beta. induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by. . .

DETD The inventive compounds **inhibit** **IL-1** signal transduction, and are therefore considered as **IL-1 antagonists**. A review article entitled "Mechanisms of Disease: The Role of Interleukin-1 in Disease" (Dinarello et al., N. Engl. J. Med.,. . . disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds are **IL-1** **antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.

DETD . . . of molecules that have a role in homeostasis. The present inventive compounds address the need identified by Dinarello et al. **inhibiting** **IL-1** cellular signaling.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1** **antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . with ulcerative colitis, and tissue concentrations of IL-1.beta. and IL-8 are high in patients with inflammatory bowel disease. Therefore, an **IL-1** **antagonist**, such as the inventive compounds, is effective to treat inflammatory bowel disease.

DETD . . . IL-1.beta. also stimulates production of PDGF. Taken together, IL-1.beta. plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1**.beta. **antagonist**, such as the inventive compounds is useful in preventing and treating atherosclerosis.

DETD . . . the antitumor effect of a non-alkylating antitumor agent; (15) to inhibit the production of osteoclast activating factor in response to **IL-1**.beta.; (16) **inhibit** degranulation in response to IgE; (17) enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter,. . .

DETD In an assay measuring inhibitive effects in a PDGF/lL-1 .beta. co-stimulation, proliferation assay, a group of compounds showed **inhibitive** properties. The PDGF/**IL-1** .beta. assay is useful in measuring in vitro activity, indicative of therapeutic potential for treating or preventing restenosis and reperfusion.. . .

DETD . . . amount of fluorescence remaining analyzed on a fluorescence plate reader. The results, reported in FIGS. 62A and 62B (TNF.alpha. or **IL-1**.beta., respectively), show **inhibition** of THP-1 adhesion to HUVEC.

DETD This example illustrates an ability of the compounds to **inhibit** both **IL-1**.alpha. or **IL**-6-stimulated proliferation of D10(N4)M or B9 cells, respectively. Using procedures similar to those discussed in the foregoing examples, cultures of

D10(N4)M. . .

L11 ANSWER 22 OF 36 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	97:40793 USPATFULL	
TITLE:	Treatment of diseases using enantiomerically pure hydroxylated xanthine compounds	
INVENTOR(S):	Bianco, James A., Seattle, WA, United States Woodson, Paul, Bothell, WA, United States Porubek, David, Edmonds, WA, United States Singer, Jack, Seattle, WA, United States	
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)	

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5629315		19970513	<--
APPLICATION INFO.:	US 1995-456900		19950601 (8)	
DISCLAIMER DATE:	20150601			
RELATED APPLN. INFO.:	Division of Ser. No. US 1994-343810, filed on 22 Nov 1994, now abandoned which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994, now abandoned which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Criares, Theodore J.			
LEGAL REPRESENTATIVE:	Faciszewski, Stephen			
NUMBER OF CLAIMS:	5			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	22 Drawing Figure(s); 22 Drawing Page(s)			
LINE COUNT:	1736			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5629315 19970513 <--

DRWD . . . interleukin-2 (IL-2). CT1501R was added to the cells at the doses indicated two hours prior to activation with ConA and **IL**-1.alpha. or **IL**-2. CT1501R **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 3. Background counts were less than 200 cpm.

DRWD . . . factor) and IL-1. CT1501R and PTX were separately added to the cells two hours prior to activation with PDGF and **IL-1**. Both drugs **inhibited** smooth muscle cell proliferation at the higher doses tested as shown in FIG. 4. CT1501R was more active than PTX.

DRWD FIG. 19 shows **inhibition** of **IL**-1-.alpha. release in LPS activated PEC by CT1501R. Cells were isolated and treated with or without 250 .mu.M CT1501R one hour. . .

DRWD FIG. 20 shows **inhibition** of TNF-.alpha. release from **IL-1**-.alpha.-activated mouse peritoneal macrophages. Cells were isolated and treated with or without CT1501R (250 .mu.M) 1 hour prior to IL-1-.alpha. activation.. . .

DETD . . . up regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells of CD18 in neutrophils; (3) **inhibiting** TNF and **IL-1** induced metalloproteases (an inflammation model); (4) block LPS-induced cellular activation (for prevention and treatment of septic shock); (5) suppress T. . .

DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, CT1501R reduced PUMP-1 activity induced by 100 U/ml of. . .

DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A recent review article entitled "The Role of Interleukin-1 in Disease" (Dinarello and Wolff N. Engl. J. Med. 328, 106,. . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.

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DETD . . . interleukin-2 (IL-2). CT1501R was added to the cells at the doses indicated two hours prior to activation with ConA and **IL-1**.alpha. or **IL-2**. CT1501R **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 3. Background counts were less than 200 cpm.

DETD . . . factor) and IL-1. CT1501R and PTX were separately added to the cells two hours prior to activation with PDGF and **IL-1**. Both drugs **inhibited** smooth muscle cell proliferation at the higher doses tested as shown in FIG. 4 with CT1501R being more active

than. . .
DETD CT1501R **inhibited** LPS, TNF-.alpha. and **IL-1** .alpha.-mediated inflammatory signaling pathways and concomitant cellular responses in peritoneal macrophages, the human U937 histiocytic leukemia cell line, and in human. . . LPS. The IC50 for TNF-.alpha. inhibition using 10 .mu.g/ml LPS stimulation was approximately 30 .mu.M. CT1501R blocked TNF-.alpha. release from **IL-1**.alpha. activated PEC. CT1501R **inhibited** the increase in adhesion of U937 cells to TNF-.alpha., IL-1.alpha. or LPS activated HUVEC. Finally, CT1501R **inhibited** **IL-1**.alpha.-induced activation and increased adhesiveness of U937 cells to non-stimulated HUVEC.

L11 ANSWER 23 OF 36 USPATFULL
AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	97:31820 USPATFULL
TITLE:	Process for preparing enantiomerically pure xanthine derivatives
INVENTOR(S):	Bianco, James A., Seattle, WA, United States Woodson, Paul, Bothell, WA, United States Porubek, David, Edmonds, WA, United States Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5621102		19970415	<--
APPLICATION INFO.:	US 1995-456897		19950601 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994, now abandoned which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994, now abandoned which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Rotman, Alan L.
LEGAL REPRESENTATIVE:	Faciszewski, Stephen
NUMBER OF CLAIMS:	10
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT:	1763

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5621102 19970415 <--
DRWD . . . interleukin-2 (IL-2). CT1501R was added to the cells at the doses indicated two hours prior to activation with ConA and **IL** **-1**.alpha. or **IL**-2. CT1501R **inhibited**

thymocyte proliferation in a dose-response manner as is shown in FIG. 3. Background counts were less than 200 cpm.

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DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

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thus moderation or prevention of. . .

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DETD . . . factor) and IL-1. CT1501R and PTX were separately added to the cells two hours prior to activation with PDGF and **IL-1** . Both drugs **inhibited** smooth muscle cell proliferation at the higher doses tested as shown in FIG. 4 with CT1501R being more active than. . .

DETD CT1501R **inhibited** LPS, TNF-.alpha. and **IL-1** .alpha.-mediated inflammatory signaling pathways and concomitant cellular responses in peritoneal macrophages, the human U937 histiocytic leukemia cell line, and in human. . . LPS. The IC50 for TNF-.alpha. inhibition using 10 .mu.g/ml LPS stimulation was approximately 30 .mu.M. CT1501R blocked TNF-.alpha. release from **IL-1**.alpha. activated PEC. CT1501R **inhibited** the increase in adhesion of U937 cells to TNF-.alpha., IL-1.alpha. or LPS activated HUVEC. Finally, CT1501R **inhibited** **IL-1**.alpha.-induced activation and increased adhesiveness of U937 cells to non-stimulated HUVEC.

L11 ANSWER 24 OF 36 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in treating inflammatory disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	97:31706 USPATFULL
TITLE:	Enatiomerically pure hydroxylated xanthine compounds to treat inflammatory diseases
INVENTOR(S):	Bianco, James A., Seattle, WA, United States Woodson, Paul, Bothell, WA, United States Porubek, David, Edmonds, WA, United States Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5620984		19970415	<--
APPLICATION INFO.:	US 1995-456898		19950601 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994 which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994 which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Criares, Theodore J.
LEGAL REPRESENTATIVE:	Faciszewski, Stephen, Oster, Jeffrey B.
NUMBER OF CLAIMS:	3

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1721
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5620984 19970415 <--
DRWD . . . interleukin-2 (IL-2). CT1501R was added to the cells at the doses indicated two hours prior to activation with ConA and IL-**1** .alpha. or **IL**-2. CT 1501R **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 3. Background counts were less than 200 cpm.
DRWD . . . factor) and IL-1. CT1501R and PTX were separately added to the cells two hours prior to activation with PDGF and **IL-1** . Both drugs **inhibited** smooth muscle cell proliferation at the higher doses tested as shown in FIG. 4. CT1501R was more active than PTX.
DRWD FIG. 19 shows **inhibition** of **IL-1**-.alpha. release in LPS activated PEC by CT1501R. Cells were isolated and treated with or without 250 .mu.M CT1501R one hour. . .
DRWD FIG. 20 shows **inhibition** of TNF-.alpha. release from **IL-1**-.alpha.-activated mouse peritoneal macrophages. Cells were isolated and treated with or without CT1501R (250 .mu.M) 1 hour prior to IL-1-.alpha. activation.. . .
DETD . . . up regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells of CD18 in neutrophils; (3) **inhibiting** TNF and **IL-1** induced metalloproteases (an inflammation model); (4) block LPS-induced cellular activation (for prevention and treatment of septic shock); (5) suppress T. . .
DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, CT1501R reduced PUMP-1 activity induced by 100 U/ml of. . .
DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A recent review article entitled "The Role of Interleukin-1 in Disease" (Dinarello and Wolff N. Engl. J. Med. 328, 106,. . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.
DETD . . . of molecules that have a role in homeostasis." The present inventive compounds address the need identified by Dr. Denarello by **inhibiting** cellular signaling only through the **IL-1** Type I receptor and not through the IL-1 Type II receptor.
DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.
DETD . . . with ulcerative colitis, and tissue concentrations of IL-1 and IL-8 are high in patients with inflammatory bowel disease. Therefore, an **IL-1 antagonist**, such as the inventive compounds, would be effective to treat inflammatory bowel disease.
DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1

plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

DETD . . . interleukin-2 (IL-2). CT1501R was added to the cells at the doses indicated two hours prior to activation with ConA and **IL-1**.alpha. or **IL**-2. CT1501R **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 3. Background counts were less than 200 cpm.

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DETD CT1501R **inhibited** LPS, TNF-.alpha. and **IL-1**.alpha.-mediated inflammatory signaling pathways and concomitant cellular responses in peritoneal macrophages, the human U937 histiocytic leukemia cell line, and in human. . . LPS. The IC50 for TNF-.alpha. inhibition using 10 .mu.g/ml LPS stimulation was approximately 30 .mu.M. CT1501R blocked TNF-.alpha. release from **IL-1**.alpha. activated PEC. CT1501R **inhibited** the increase in adhesion of U937 cells to TNF-.alpha., IL-1.alpha. or LPS activated HUVEC. Finally, CT1501R **inhibited IL-1**.alpha.-induced activation and increased adhesiveness of U937 cells to non-stimulated HUVEC.

L11 ANSWER 25 OF 36 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 97:22792 USPATFULL

TITLE: Enantiomerically pure hydroxylated xanthine compounds to treat shock symptoms

INVENTOR(S): Bianco, James A., Seattle, WA, United States
Woodson, Paul, Bothell, WA, United States
Porubek, David, Edmonds, WA, United States
Singer, Jack, Seattle, WA, United States

PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5612349		19970318	<--
APPLICATION INFO.:	US 1995-457062		19950601 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994, now abandoned which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994, now abandoned which

is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: Faciszewski, Stephen
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1725
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5612349 19970318 <--

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DRWD FIG. 19 shows **inhibition** of **IL-1**-.alpha. release in LPS activated PEG by CT1501R. Cells were isolated and treated with or without 250 .mu.M CT1501R one hour. . .

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DRWD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

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DRWD . . . 1L-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

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L11 ANSWER 26 OF 36 USPATFULL

AB Them is disclosed compounds and pharmaceutical compositions that is R enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in treating the side effects of immunosuppressive agent and interleukin-2 therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	96:111463 USPATFULL
TITLE:	Enatiomerically pure hydroxylated xanthine compounds
INVENTOR(S):	Bianco, James A., Seattle, WA, United States Woodson, Paul, Bothell, WA, United States Porubek, David, Edmonds, WA, United States Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5580874		19961203	<--
APPLICATION INFO.:	US 1995-457685		19950601 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994, now abandoned which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994 which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: Faciszewski, Stephen
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 1733
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5580874 19961203 <--

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L11 ANSWER 27 OF 36 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in treating proliferative vascular disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 96:111462 USPATFULL

TITLE: Enatiomerically pure hydroxylated xanthine compounds to

	treat proliferative vascular diseases
INVENTOR(S):	Bianco, James A., Seattle, WA, United States Woodson, Paul, Bothell, WA, United States Porubek, David, Edmonds, WA, United States Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5580873		19961203	<--
APPLICATION INFO.:	US 1995-456899		19950601 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994 which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994 which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Criares, Theodore J.
LEGAL REPRESENTATIVE:	Oster, Jeffrey B.
NUMBER OF CLAIMS:	3
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT:	1728

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5580873 19961203 <--

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L11 ANSWER 28 OF 36 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions that are a

resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in treating baldness.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	96:97041 USPATFULL
TITLE:	R-enatiomerically pure hydroxylated xanthine compounds to treat baldness
INVENTOR(S):	Bianco, James A., Seattle, WA, United States Woodson, Paul, Bothell, WA, United States Porubek, David, Edmonds, WA, United States Singer, Jack, Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5567704		19961022	<--
APPLICATION INFO.:	US 1995-457683		19950601 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343810, filed on 22 Nov 1994 which is a division of Ser. No. US 1994-307554, filed on 16 Sep 1994 which is a continuation of Ser. No. US 1993-13977, filed on 4 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-926665, filed on 7 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-846354, filed on 4 Mar 1992, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Criares, Theodore J.
LEGAL REPRESENTATIVE:	Oster, Jeffrey B.
NUMBER OF CLAIMS:	4
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT:	1736

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5567704 19961022 <--

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DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . with ulcerative colitis, and tissue concentrations of IL-1 and IL-8 are high in patients with inflammatory bowel disease. Therefore, an **IL-1 antagonist**, such as the inventive compounds, would be effective to treat inflammatory bowel disease.

DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

DETD . . . interleukin-2 (IL-2). CT1501R was added to the cells at the doses indicated two hours prior to activation with ConA and **IL-1**.alpha. or **IL-2**. CT1501R **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 3. Background counts were less than 200 cpm.

DETD . . . factor) and IL-1. CT1501R and PTX were separately added to the cells two hours prior to activation with PDGF and **IL-1**. Both drugs **inhibited** smooth muscle cell proliferation at the higher doses tested as shown in FIG. 4 with CT1501R being more active than. . .

DETD CT150 1 R **inhibited** LPS, TNF-.alpha. and **IL-1**.alpha.-mediated inflammatory signaling pathways and concomitant cellular responses in peritoneal macrophages, the human U937 histiocytic leukemia cell line, and in human. . . LPS. The IC50 for TNF-.alpha. inhibition using 10 .mu.g/ml LPS stimulation was approximately 30 .mu.M. CT1501R blocked TNF-.alpha. release from

IL-1.alpha. activated PEC. CT1501R **inhibited** the increase in adhesion of U937 cells to TNF-.alpha., IL-1.alpha. or LPS activated HUVEC. Finally, CT1501R **inhibited IL-1**.alpha.-induced activation and increased adhesiveness of U937 cells to non-stimulated HUVEC.

L11 ANSWER 29 OF 36 USPATFULL

AB There is disclosed an olefin-substituted compound having the formula:

R--(core moiety),

wherein R is a straignt chain hydrocarbon having at least one double bond and a carbon chain length of from about 6 to about 18 carbon atoms, wherein multiple double bonds are separated from each other by at least three carbon atoms, wherein the closest double bond to the core moiety is at least five carbon atoms from the core moiety, and wherein the hydrocarbon chain may be substituted by a hydroxyl, halo, keto or dimethylanimo group and/or interrupted by an oxygen atom and salts thereof and pharmaceutical compositions thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	96:46169 USPATFULL	
TITLE:	Olefin substituted long chain compounds	
INVENTOR(S):	Underiner, Gail, Brier, WA, United States Porubek, David, Seattle, WA, United States Klein, J. Peter, Vashon, WA, United States Eiseman, Elisa, Seattle, WA, United States Leigh, Alistair, Brier, WA, United States Kumar, Anil, Seattle, WA, United States Michnick, John, Seattle, WA, United States	
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)	

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5521315		19960528	<--
APPLICATION INFO.:	US 1993-59697		19930510 (8)	
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1993-3372, filed on 12 Jan 1993, now patented, Pat. No. US 5354756			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Shah, Mukund J.			
ASSISTANT EXAMINER:	Sripada, Pavanaram K.			
LEGAL REPRESENTATIVE:	Faciszewski, Stephen, Oster, Jeffrey B.			
NUMBER OF CLAIMS:	7			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	22 Drawing Figure(s); 22 Drawing Page(s)			
LINE COUNT:	2761			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5521315 19960528 <--

DRWD . . . alpha (IL-1.alpha.). CT1408 was added to the cells at the doses indicated two hours prior to activation with ConA and **IL-1**.alpha.. CT1408 **inhibited** thymocyte proliferation in a dose-response manner with an IC50 of about 19 .mu.M, as is shown in FIG. 7. Background. . .

DETD . . . regulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells of CD 18 in neutrophils; (3) **inhibiting** TNF, LPS and **IL-1** induced

metalloproteases (an inflammation model); (4) block LPS, TNF or IL-1 induced cellular activation (for prevention and treatment of septic. . .

DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by. . .

DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A recent review article entitled "The Role of interleukin-1 in Disease" (Dinarello and Wolff N. Engl. J. Med. 328, 106,. . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.

DETD . . . molecules that have a role in homeostasis." The present inventive compounds address the need identified by Dinarello and Wolff by **inhibiting** cellular signaling only through the **IL-1** Type I receptor and not through the IL-1 Type II receptor.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . with ulcerative colitis, and tissue concentrations of IL-1 and IL-8 are high in patients with inflammatory bowel disease. Therefore, an **IL-1 antagonist**, such as the inventive compounds, would be effective to treat inflammatory bowel disease.

DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

DETD . . . Proc. Natl. Acad. Sci. USA 84:4616, 1987). Therefore, the loss of E.sub.2 that accompanies menopause allows PBM to secrete more **IL-1** and E.sub.2 **inhibits IL-1** secretion. **IL-1** is one of the most potent inducers of bone resorption in vitro and in vivo. IL-1 likely originates from macrophage-lineage. . . circuitry. Therefore, both IL-1 and TNF augment bone resorption, either directly or indirectly, and a drug that is both an **IL-1** and TNF **antagonist**, should be effective for the treatment and prevention of bone loss and osteoporosis symptoms in postmenopausal women.

DETD . . . inventive compounds inhibit cellular second messenger signaling, specifically through the IL-1 and TNF type I receptors and therefore function as **IL-1** and TNF **antagonists**. Accordingly, the inventive compounds are useful for treating and preventing bone loss and osteoporosis.

DETD . . . disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

DETD . . . interleukin-2 (IL-2). CT1408 was added to the cells at the

doses indicated two hours prior to activation with ConA and **IL** **-1**.alpha.. CT1408 **inhibited** thymocyte proliferation in a dose-response manner with an IC50 of about 19 .mu.M, as is shown in FIG. 7. Background. . .

L11 ANSWER 30 OF 36 USPATFULL

AB A method of treating a mammal exposed to endotoxin in order to reduce the detrimental effects of said endotoxin, comprising administering to said mammal a therapeutically effective amount of a 2-halo-adenosine nucleotide analog. 2-Cloro-ATP is the preferred species of the 2-halo-adenosine nucleotide. The nucleotide used in this treatment inhibits lipo-polysaccharide-induced GTPase activity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	96:41201 USPATFULL
TITLE:	Method of treating endotoxin effects with 2-haloadenosine nucleotide analogs
INVENTOR(S):	Bertics, Paul J., Oregon, WI, United States Proctor, Richard A., Madison, WI, United States
PATENT ASSIGNEE(S):	Wisconsin Alumni Research Foundation, Madison, WI, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5516762		19960514	<--
APPLICATION INFO.:	US 1993-137685		19931015	(8)
DISCLAIMER DATE:	20131015			
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1992-976659, filed on 16 Nov 1992, now abandoned which is a continuation of Ser. No. US 1991-681036, filed on 5 Apr 1991, now abandoned			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Kunz, Gary L.			
LEGAL REPRESENTATIVE:	Quarles & Brady			
NUMBER OF CLAIMS:	3			
EXEMPLARY CLAIM:	1			
LINE COUNT:	583			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5516762 19960514 <--

SUMM . . . object to disclose methods of treatment of mammals to protect them from the deleterious effects of Gram-negative endotoxins and to **inhibit** the release of TNF and **IL-1**, which comprise administering to the mammals safe and effective amounts of compounds of the present invention.

DETD (3) Loss of G.I. mucosal barrier, e.g. trauma, drug-induced **mucositis**.

L11 ANSWER 31 OF 36 USPATFULL

AB A method of treating mammals to reduce the deleterious effects of endotoxin and endotoxic shock mediators comprising administering a therapeutic amount of a 2-alkylthio-adenosine-5'-nucleotide. The preferred compound is 2-methylthio-adenosine-5'-triphosphate. The nucleotide used in this treatment inhibits lipopolysaccharide-induced GTPase activity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 96:14799 USPATFULL

09/800,855

TITLE: Method of treating endotoxin effects with 2-methylthio-ATP and analogs
INVENTOR(S): Bertics, Paul J., Oregon, WI, United States
Proctor, Richard A., Madison, WI, United States
PATENT ASSIGNEE(S): Wisconsin Alumni Research Foundation, Madison, WI, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5492898		19960220	<--
APPLICATION INFO.:	US 1993-137326		19931015 (8)	

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1992-976659, filed on 16 Nov 1992, now abandoned which is a continuation of Ser. No. US 1991-681036, filed on 5 Apr 1991, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Kunz, Gary L.
LEGAL REPRESENTATIVE: Quarles & Brady
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
LINE COUNT: 669
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5492898 19960220 <--
SUMM . . . object to disclose methods of treatment of mammals to protect them from the deleterious effects of Gram-negative endotoxins and to **inhibit** the release of TNF and **IL-1**, which comprise administering to the mammals safe and effective amounts of compounds of the present invention. ##STR1##
DETD (3) Loss of G.I. mucosal barrier, e.g. trauma, drug -induced **mucositis**.

L11 ANSWER 32 OF 36 USPATFULL
AB There is disclosed compounds and pharmaceutical compositions comprising compounds of the formula: ##STR1## wherein each of one or two R is independently ##STR2## wherein n is an integer from 7 to 20, at least one of X or Y is --OH and if one of X or Y is --OH then the other X or Y is H, CH.sub.3, CH.sub.3 --CH.sub.2, CH.sub.3 --(CH.sub.2).sub.2 --, or (CH.sub.3).sub.2 --CH.sub.2 --, and W.sub.1, W.sub.2, and W.sub.3 is independently H, CH.sub.3, CH.sub.3 --CH.sub.2, CH.sub.3 --(CH.sub.2).sub.2 --, or (CH.sub.3).sub.2 --CH.sub.2 --, and wherein the alkyl groups may be substituted by a hydroxyl, halo or dimethylamino group and/or interrupted by an oxygen atom, H or alkyl (1-4C), including resolved enantiomers and/or diastereomers, salts and mixtures thereof. In particular, the compounds lower elevated levels of unsaturated, non-arachidonate phosphatidic acid (PA) and diacylglycerol (DAG) derived from said PA within seconds of the primary stimulus and their contact with said cells. The modulatory effect depends on the nature of the target cell and the stimulus applied.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 95:108287 USPATFULL
TITLE: Substituted long chain alcohol xanthine compounds
INVENTOR(S): Underiner, Gail, Brier, WA, United States
Porubek, David, Edmonds, WA, United States
Klein, J. Peter, Vashon Island, WA, United States
Woodson, Paul, Bothell, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States

(U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5473070		19951205	<--
APPLICATION INFO.:	US 1992-976353		19921116 (7)	

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shah, Mukund J.
ASSISTANT EXAMINER: Sripada, P. K.
LEGAL REPRESENTATIVE: Faciszewski, Stephen, Oster, Jeffrey B.
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT: 890
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5473070 19951205 <--
SUMM . . . of metalloproteases in synovial cells, other fibroblasts and a glomerular epithelial cell in response to inflammatory stimuli, such as TNF, **IL-1** and the like, to **inhibit** production of osteoclast-activating factor (OAP) by osteoclasts in response to **IL-1**; to **inhibit** degranulation of mast cells and basophils in response to IgE; to modulate signal transduction of the neurotransmitters epinephrine and acetylcholine. . .
DETD . . . tumor burden, a hormone-related disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

L11 ANSWER 33 OF 36 USPATFULL
AB Therapeutic compounds have the formula:

(X)j-(non-cyclic core moiety),

j being an integer from one to three, the core moiety is non-cyclic and X is a racemic mixture, R or S enantiomer, solvate, hydrate, or salt of: ##STR1## *C is a chiral carbon atom, n is an integer from one to four (preferably from one to three), one or more carbon atoms of (CH.sub.2).sub.n may be substituted by a keto or hydroxy group, and m is an integer from one to fourteen. Independently, R.sub.1 and R.sub.2 may be a hydrogen, a straight or branched chain alkane or alkene of up to twelve carbon atoms in length, or --(CH.sub.2).sub.w R.sub.5, w being an integer from two to fourteen and R.sub.5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R.sub.5 being hydroxy, chloro, fluoro, bromo, or C.sub.1-6 alkoxy. Or jointly, R.sub.1 and R.sub.2 form a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms, N being a hetero atom. R.sub.3 is a hydrogen or C.sub.1-3. Or, therapeutic compounds may also have the formula: ##STR2## R.sub.4 is a hydrogen, a straight or branched chain alkane or alkene of up to eight carbon atoms in length, --(CH.sub.2).sub.w R.sub.5, w being an integer from two to fourteen and R.sub.5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R.sub.5 being hydroxy, chloro, fluoro, bromo, or C.sub.1-6 alkoxy, or a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight

carbon atoms. r and s are independently integers from one to four, the sum (r+s) not being greater than five. t is an integer from one to fourteen and one or more carbon atoms of (CH.sub.2).sub.s or (CH.sub.2).sub.t may be substituted by a keto or hydroxy group.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	95:105868 USPATFULL
TITLE:	Cell signaling inhibitors
INVENTOR(S):	Michnick, John, Seattle, WA, United States Underiner, Gail E., Brier, WA, United States Klein, J. Peter, Vashon Island, WA, United States Rice, Glenn C., Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5470878		19951128	<--
APPLICATION INFO.:	US 1993-164081		19931208 (8)	
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1993-40820, filed on 31 Mar 1993, now abandoned			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Kumar, Shailendra			
LEGAL REPRESENTATIVE:	Faciszewski, Stephen, Oster, Jeffrey B.			
NUMBER OF CLAIMS:	10			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	43 Drawing Figure(s); 42 Drawing Page(s)			
LINE COUNT:	2665			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5470878 19951128 <--

DRWD . . . reports inhibitive activity results for inventive compounds nos. 27, 28, 32, 30, 31, 32 and 34 in an assay measuring **inhibitive** effects in a PDGF/**IL-1** co-stimulation.

DETD . . . kidney mesengial cells; (2) suppress upregulation of adhesion molecules as shown, for example, by blocking VCAM in endothelial cells; (3) **inhibit** TNF, LPS and **IL-1** induced metalloproteases (an inflammation model); (4) block LPS, TNF or IL-1 induced metalloprotease and secondary cytokine production (for prevention and. . .

DETD . . . type IV collagenase that is usually constitutive and induced by TNF or IL-1, and a stromelysin/PUMP-1 induced by TNF and **IL-1**. The inventive compounds can **inhibit** TNF or **IL-1** induction of the 92 kD type V gelatinase inducable metalloprotease. Moreover, the inventive compounds can reduce PUMP-1 activity induced by. . .

DETD The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as **IL-1 antagonists**. A recent review article entitled "The Role of Interleukin-1 in Disease" (Dinarello et al., N. Engl. J. Med. (1993) 106:328). . . periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds **inhibit** cellular signaling through the **IL-1** Type I receptor and are **IL-1 antagonists**, the inventive compounds are useful for treating all of the above-mentioned diseases.

DETD . . . molecules that have a role in homeostasis. The present

inventive compounds address the need identified by Dinarello and Wolff by **inhibiting** cellular signaling only through the **IL-1** Type I receptor and not through the IL-1 Type II receptor.

DETD . . . as well as phospholipases and cyclooxygenase, and blocking its action reduces bacterial-cell-wall-induced arthritis in rats." Therefore, the inventive compounds, as **IL-1 antagonists**, are useful to treat and prevent rheumatoid arthritis.

DETD . . . with ulcerative colitis, and tissue concentrations of IL-1 and IL-8 are high in patients with inflammatory bowel disease. Therefore, an **IL-1 antagonist**, such as the inventive compounds, would be effective to treat inflammatory bowel disease.

DETD . . . IL-1 also stimulates production of PDGF. Taken together, IL-1 plays a part in the development of atherosclerotic lesions. Therefore, an **IL-1 antagonist**, such as the inventive compounds should be useful in preventing and treating atherosclerosis.

DETD . . . the antitumor effect of a nonalkylating antitumor agent, (18) to inhibit the production of osteoclast activating factor in response to **IL-1**, (19) **inhibit** degranulation in response to IgE, (20) enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter,. . .

DETD . . . an autoimmune disease, inflammation, restenosis, coronary artery disease, atherosclerosis, hypertension, unwanted immune response (such as allograft reactions), viral infection, nephritis, **mucositis**, and various allergic responses. Allergic responses include acute allergic response and thus rhinorrhea, sinus dminage, diffuse tissue edema, and generalized. . .

DETD In an assay measuring **inhibitive** effects in a PDGF/**IL-1** co-stimulation, proliferation assay, a group of inventive compounds showed **inhibitive** properties. The PDGF/**IL-1** assay is useful in measuring in vitro activity, indicative of therapeutic potential for treating or preventing restenosis and reperfusion. FIG.. . .

L11 ANSWER 34 OF 36 USPATFULL

AB There is disclosed compounds and pharmaceutical compositions having a xanthine core of the formula: ##STR1## wherein each of one or two R is independently ##STR2## wherein n is an integer from about 3 to about 18 forming a hydrocarbon chain, wherein the hydrocarbon chain may have one or more double bonds (preferably in a cis configuration), and may be substituted by a hydroxyl, halo or dimethylamino group and/or interrupted by an oxygen atom. The compounds lower elevated levels of unsaturated, non-arachidonate phosphatidic acid (PA) and diacylglycerol (DAG) derived from said PA within seconds of the primary stimulus and their contact with cells. The modulatory effect depends on the nature of the target cell and the stimulus applied.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	95:71491 USPATFULL
TITLE:	Acetal or ketal substituted xanthine compounds
INVENTOR(S):	Leigh, Alistair, Edmonds, WA, United States Underiner, Gail, Brier, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

NUMBER	KIND	DATE

PATENT INFORMATION: US 5440041 19950808 <--
APPLICATION INFO.: US 1994-194135 19940208 (8)
RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-4353, filed on 14 Jan 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shah, Mukund J.
ASSISTANT EXAMINER: Sripada, Pavanaram K.
LEGAL REPRESENTATIVE: Faciszewski, Stephen, Oster, Jeffrey B.
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 874
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5440041 19950808 <--
DRWD . . . alpha (IL-1.alpha.). CT1567 was added to the cells at the doses indicated two hours prior to activation with ConA and **IL-1**.alpha.. CT1567 **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 2. Background counts were less than 200 cpm.
DETD . . . tumor burden, a hormone-related disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis**, and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .
DETD . . . in a liquid scintillation counter. Drug was added at the doses indicated two hours prior to activation with ConA and **IL-1**.alpha.. CT1567 **inhibited** thymocyte proliferation in a dose-response manner as is shown in FIG. 2. Background counts were less than 200 cpm.

L11 ANSWER 35 OF 36 USPATFULL
AB Compounds of the formula ##STR1## wherein each of one or two R is independently ##STR2## wherein n is an integer from 4 to 18, each R.sub.1 ' and R.sub.2 ' is independently H, alkyl (1-4C) or alkenyl (1-4C); and R.sub.3 ' and R.sub.4 ' are independently H or CH.sub.3 ; and wherein the alkyl or alkenyl may be substituted by a hydroxyl, halo or dimethylamino group and/or interrupted by an oxygen atom, H or alkyl (1-4C), including resolved enantiomers and/or diastereomers and mixtures thereof. Preferably, n is from 6 to 10, R.sub.1 ' and R.sub.2 ' are independently H or methyl and R.sub.3 ' and R.sub.4 ' are H. In particular, the compounds lower elevated levels of unsaturated, non-arachidonate phosphatidic acid (PA) and diacylglycerol (DAG) derived from said PA within seconds of the primary stimulus and their contact with said cells. The modulatory effect depends on the nature of the target cell and the stimulus applied.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 94:73300 USPATFULL
TITLE: Substituted aminoalkyl xanthine compounds
INVENTOR(S): Klein, J. Peter, Vashon, WA, United States
Underiner, Gail, Bothell, WA, United States
Leigh, Alistair, Edmonds, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

NUMBER KIND DATE

PATENT INFORMATION:	US 5340813	19940823	<--
APPLICATION INFO.:	US 1992-973804	19921109 (7)	
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Shah, Mukund J.		
ASSISTANT EXAMINER:	Sripada, P. K.		
LEGAL REPRESENTATIVE:	Oster, Jeffrey B.		
NUMBER OF CLAIMS:	7		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	7 Drawing Figure(s); 7 Drawing Page(s)		
LINE COUNT:	725		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5340813 19940823 <--

SUMM . . . of metalloproteases in synovial cells, other fibroblasts and a glomerular epithelial cell in response to inflammatory stimuli, such as TNF, **IL-1** and the like, to **inhibit** production of osteoclast-activating factor (OAP) by osteoclasts in response to **IL-1**; to **inhibit** degranulation of mast cells and basophils in response to IgE; to modulate signal transduction of the neurotransmitters epinephrine and acetylcholine. . .

DRWD FIG. 6 shows a thymocyte proliferation assay wherein thymocyte proliferation is stimulated by Con A and **IL-1** .alpha.. Both CT1521 and CT1558 **inhibited** proliferation in thymocytes.

DETD . . . tumor burden, a hormone-related disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis** , and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

L11 ANSWER 36 OF 36 USPATFULL

AB Compounds of the formula ##STR1## including the resolved enantiomers and/or diastereomers and mixtures thereof wherein each of one or two R is independently ##STR2## wherein n is 1-16 and R' is H or alkyl(1-4C); and wherein each remaining R is independently H, alkyl(1-6C), alkenyl(1-6C) or benzyl; an wherein said alkyl or alkenyl may be substituted by a hydroxyl, halo, or dimethylamino group, and/or interrupted by an oxygen atom, are useful in modulating the effects of internal and external stimuli on cells by reversing the effects of these stimuli on the short-term secondary messenger pathways. In particular, the compounds lower elevated levels of unsaturated, non-arachidonate phosphatidic acid (PA) and diacylglycerol (DAG) derived from said PA within seconds of the primary stimulus and their contact with said cells. The modulatory effect depends on the nature of the target cell and the stimulus applied.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	94:15745 USPATFULL
TITLE:	Substituted epoxyalkyl xanthines
INVENTOR(S):	Klein, J. Peter, Vashon, WA, United States Porubek, David, Edmonds, WA, United States Rice, Glenn C., Seattle, WA, United States Woodson, Paul, Bothell, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5288721		19940222	<--
APPLICATION INFO.:	US 1992-949330		19920922	(7)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Ford, John M.			
ASSISTANT EXAMINER:	Sripada, P. K.			
LEGAL REPRESENTATIVE:	Oster, Jeffrey B., Murashige, Kate H.			
NUMBER OF CLAIMS:	12			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 5 Drawing Page(s)			
LINE COUNT:	945			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5288721 19940222 <--

SUMM . . . response to a nonalkylating antitumor agent, to suppress the production of metalloproteases in a glomerular epithelial cell in response to **IL-1**, to **inhibit** production of osteoclast-activating factor (OAP) by osteoclasts in response to **IL-1**, to **inhibit** degranulation of mast cells and basophils in response to IgE, to modulate signal transduction of the neurotransmitters epinephrine and acetylcholine. . .

DETD . . . tumor burden, a hormone-related disorder, a neurological disorder, an autoimmune disease, inflammation, restenosis, hypertension, unwanted immune response, viral infection, nephritis, **mucositis** , and various allergic responses. Prevention of allergic responses include prevention of acute allergic response and thus moderation or prevention of. . .

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     (FILE 'HOME' ENTERED AT 17:43:44 ON 09 FEB 2002)

     FILE 'CAPLUS, USPATFULL' ENTERED AT 17:44:01 ON 09 FEB 2002
L1         1053 S IL(2A)6(5A)(INHIBITOR? OR ANTAGONIST?)
L2            9 S L1 AND MUCOSIT?
L3            9 DUP REM L2 (0 DUPLICATES REMOVED)
L4         1672 S THALIDOMIDE
L5           22 S L4 AND MUCOSIT?
L6            3 S THALIDOMIDE(P) MUCOSIT?
L7           22 DUP REM L5 (0 DUPLICATES REMOVED)
L8         7309 S (IL(2A)1(5A)(INHIBIT? OR ANTAGONIST?) OR INTERFERON(2A)GAMMA(
L9           60 S L8 AND MUCOSITI?
L10          60 DUP REM L9 (0 DUPLICATES REMOVED)
L11          36 S L10 AND PY<=1998

=> s tilg, ?/au
L12          50 TILG, ?/AU

=> s l12 and mucosit?
L13           1 L12 AND MUCOSIT?

=> d l13 abs ibib kwic 1

L13  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
AB   Pentoxifylline (PTX) has recently been shown to modulate TNF-.alpha.
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prodn. and to reduce the incidence and severity of all major complications after bone marrow transplantation (BMT), including **mucositis**, venoocclusive disease, renal insufficiency, hypertension, and graft-vs.-host disease. To analyze in detail the effect of PTX on immune complications after BMT, the authors investigated the immunomodulatory effect of PTX on immune responses in vitro. The continuous presence of PTX significantly reduced the proliferative response of PBMC to PHA stimulation and to alloantigens in a dose-dependent manner. Starting at concns. of 100 .mu.g/mL, PTX was able to inhibit and, at 1000 .mu.g/mL, completely block mitogen-induced proliferation. Maximal inhibition of more than 90% (91 .+-. 4%) was also obsd. at PTX concns. of 1000 .mu.g/mL in the mixed lymphocyte culture (MLR) and by addn. on day 0. However, lower but still significant suppression (13 .+-. 7%) was achieved at concns. of 10 .mu.g/mL PTX. The inhibitory capacity of PTX was increased by mAbs against TNF-.alpha. (34 .+-. 5% addnl. suppression at 100 .mu.g/mL PTX) and not reversed by the addn. of rTNF-.alpha.. The effect of PTX on the generation of CTLs in vitro was studied in the cell-mediated lymphotoxicity assay. PTX (100 .mu.g/mL) significantly inhibited (P = 0.0178) the in vitro generation of CTLs when PTX was added to the culture on day 0. PTX also showed profound modulatory properties in the NK assay, with a redn. of 23 .+-. 3% in specific lysis at 10 .mu.g/mL PTX and maximal redns. of 88 .+-. 3% at 1000 .mu.g/mL PTX. Immunomodulatory properties of PTX were not only assocd. with blockage of TNF-.alpha., as shown by decreased mRNA expression and TNF-.alpha. values in the culture supernatants, but also with an impaired prodn. of other cytokines and secondary messages such as IFN-.gamma. and neopterin. PTX treatment, however, did not affect IFN-.alpha. or IL-1.beta. prodn., and IL-6 release was even increased. PTX, therefore, has profound immunomodulatory properties in vitro, which are assocd. with selective inhibition of cytokine release and can be enhanced by the addn. of mAbs against TNF-.alpha., but not reversed by the addn. of rTNF-.alpha..

ACCESSION NUMBER: 1994:124446 CAPLUS
DOCUMENT NUMBER: 120:124446
TITLE: Immune response modulation by pentoxifylline in vitro
AUTHOR(S): **Tilg, Herbert**; Eibl, Brigitte; Pichl, Marion; Gaechter, Anne; Herold, Manfred; Brankova, Juliana; Huber, Christoph; Niederwieser, Dietger
CORPORATE SOURCE: Dep. Intern. Med., Univ. Hosp., Innsbruck, 6020, Austria
SOURCE: Transplantation (1993), 56(1), 196-201
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English

AU **Tilg, Herbert**; Eibl, Brigitte; Pichl, Marion; Gaechter, Anne; Herold, Manfred; Brankova, Juliana; Huber, Christoph; Niederwieser, Dietger

AB Pentoxifylline (PTX) has recently been shown to modulate TNF-.alpha. prodn. and to reduce the incidence and severity of all major complications after bone marrow transplantation (BMT), including **mucositis**, venoocclusive disease, renal insufficiency, hypertension, and graft-vs.-host disease. To analyze in detail the effect of PTX on immune complications after BMT, the authors investigated the immunomodulatory effect of PTX on immune responses in vitro. The continuous presence of PTX significantly reduced the proliferative response of PBMC to PHA stimulation and to alloantigens in a dose-dependent manner. Starting at concns. of 100 .mu.g/mL, PTX was able to inhibit and, at 1000 .mu.g/mL, completely block mitogen-induced proliferation. Maximal inhibition of more than 90% (91 .+-. 4%) was also obsd. at PTX concns. of 1000 .mu.g/mL

in the mixed lymphocyte culture (MLR) and by addn. on day 0. However, lower but still significant suppression (13 .+-. 7%) was achieved at concns. of 10 .mu.g/mL PTX. The inhibitory capacity of PTX was increased by mAbs against TNF-.alpha. (34 .+-. 5% addnl. suppression at 100 .mu.g/mL PTX) and not reversed by the addn. of rTNF-.alpha.. The effect of PTX on the generation of CTLs in vitro was studied in the cell-mediated lymphotoxicity assay. PTX (100 .mu.g/mL) significantly inhibited (P = 0.0178) the in vitro generation of CTLs when PTX was added to the culture on day 0. PTX also showed profound modulatory properties in the NK assay, with a redn. of 23 .+-. 3% in specific lysis at 10 .mu.g/mL PTX and maximal redns. of 88 .+-. 3% at 1000 .mu.g/mL PTX. Immunomodulatory properties of PTX were not only assocd. with blockage of TNF-.alpha., as shown by decreased mRNA expression and TNF-.alpha. values in the culture supernatants, but also with an impaired prodn. of other cytokines and secondary messages such as IFN-.gamma. and neopterin. PTX treatment, however, did not affect IFN-.alpha. or IL-1.beta. prodn., and IL-6 release was even increased. PTX, therefore, has profound immunomodulatory properties in vitro, which are assocd. with selective inhibition of cytokine release and can be enhanced by the addn. of mAbs against TNF-.alpha., but not reversed by the addn. of rTNF-.alpha..

=>

09/800,855

=> s minocycline and mucosit?
L14 6 MINOCYCLINE AND MUCOSIT?

=> d l14 abs ibib kwic 1-6

L14 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2002 ACS
AB A method of reducing or inhibiting **mucositis** in a patient includes administering an inflammatory cytokine inhibitor or a mast cell inhibitor, or a combination thereof.
ACCESSION NUMBER: 1999:594911 CAPLUS
DOCUMENT NUMBER: 131:209126
TITLE: Methods and compositions using inflammatory cytokine inhibitors and mast cell inhibitors for treating and preventing **mucositis**
INVENTOR(S): Sonis, Stephen T.; Fey, Edward G.
PATENT ASSIGNEE(S): Mucosal Therapeutics Llc, USA
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9945910	A2	19990916	WO 1999-US5437	19990312
WO 9945910	A3	20000210		
W: AU, BR, CA, IL, JP, MX, NZ, PL				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9930837	A1	19990927	AU 1999-30837	19990312
BR 9908857	A	20001031	BR 1999-8857	19990312
EP 1064001	A2	20010103	EP 1999-912467	19990312
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 2001011097	A1	20010802	US 2001-800855	20010307

PRIORITY APPLN. INFO.:
US 1998-77977 P 19980313
US 1998-65012 A 19980423
US 1999-265299 A 19990309
WO 1999-US5437 W 19990312

TI Methods and compositions using inflammatory cytokine inhibitors and mast cell inhibitors for treating and preventing **mucositis**
AB A method of reducing or inhibiting **mucositis** in a patient includes administering an inflammatory cytokine inhibitor or a mast cell inhibitor, or a combination thereof.
ST inflammatory cytokine inhibitor **mucositis** treatment; mast cell inhibitor **mucositis** treatment
IT Mucous membrane
(disease, inflammation; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)
IT Drug delivery systems
(gels, oral; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)
IT Anti-inflammatory agents
Antihistamines
Antimicrobial agents

Antiulcer agents
Drug delivery systems
Mast cell
Mouthwashes
(inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Cytokines
Interleukin 1
Interleukin 6
Tumor necrosis factors
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Tetracyclines
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Drug delivery systems
(lozenges; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Cell degranulation
(mast cell, inhibitors; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Stomach, disease
(mucosa, injury; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Antitumor agents
Chemotherapy
Radiotherapy
(**mucositis** induced by; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Inflammation
(mucous membrane; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Anti-inflammatory agents
(nonsteroidal; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Drug delivery systems
(oral; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Drug delivery systems
(pastes, oral; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Mouth
(stomatitis; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Drug delivery systems
(tablets; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT Interferons
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(.gamma.; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT 39391-18-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(1 and 2, inhibitors; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT 50-35-1, Thalidomide 53-86-1, Indomethacin 79-17-4, Aminoguanidine 113-00-8, Guanidine 5104-49-4, Flurbiprofen 10118-90-8, **Minocycline**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

IT 10102-43-9, Nitric oxide, biological studies 37259-58-8, Serine protease 141907-41-7, Matrix metalloproteinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; inflammatory cytokine inhibitors, mast cell inhibitors, and other agents for treating and preventing **mucositis**)

L14 ANSWER 2 OF 6 USPATFULL

AB In accordance with the present invention, there are provided conjugates of physiologically compatible free radical scavengers (e.g., dithiocarbamate disulfides (DD)) and pharmacologically active agents (e.g., NSAIDS). Invention conjugates provide a new class of pharmacologically active agents (e.g., anti-inflammatory agents) which cause a much lower incidence of side-effects due to the protective effects imparted by modifying the pharmacologically active agents as described herein. In addition, invention conjugates are more effective than unmodified pharmacologically active agents because cells and tissues contacted by the pharmacologically active agent(s) are protected from the potentially damaging effects of free radical overproduction induced thereby as a result of the co-production of free radical scavenger (e.g., dithiocarbamate), in addition to free pharmacologically active agent, when invention conjugate is cleaved.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2001:131342 USPATFULL
TITLE:	Conjugates of dithiocarbamate disulfides with pharmacologically active agents and uses therefor
INVENTOR(S):	Lai, Ching-San, Encinitas, CA, United States Vassilev, Vassil P., San Diego, CA, United States Wang, Tingmin, San Marcos, CA, United States
PATENT ASSIGNEE(S):	Medinox, Inc., San Diego, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6274627	B1	20010814	
APPLICATION INFO.:	US 1999-416619		19991012	(9)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	GRANTED			
PRIMARY EXAMINER:	Weddington, Kevin E.			
LEGAL REPRESENTATIVE:	Reiter, Stephen E.Foley & Lardner			
NUMBER OF CLAIMS:	9			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 5 Drawing Page(s)			
LINE COUNT:	2173			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . Gianni et al., in Rev. Biochem. Toxicol. 5:1-82 (1983)). In addition to cardiomyopathy, adriamycin administration causes cutaneous irritation and alopecia, **mucositis** (stomatitis and esophagitis), phlebosclerosis and hematologic toxicities and many other local and systemic toxicities.
DETD . . . erythromycin ethylsuccinate, erythromycin, erythromycin estolate, erythromycin lactobionate, erythromycin siearate, erythromycin ethylsuccinate, and the like), tetracyclines (e.g., tetracycline hydrochloride, doxycycline hyclate, **minocycline** hydrochloride, and the like), and the like);

L14 ANSWER 3 OF 6 USPATFULL
AB A method of reducing or inhibiting **mucositis** in a patient, which includes administering an inflammatory cytokine inhibitor or a mast cell inhibitor, or a combination thereof, is disclosed

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2001:123589 USPATFULL
TITLE: Methods and compositions for treating and preventing **mucositis**
INVENTOR(S): Sonis, Stephen T., Wayland, MA, United States
Fey, Edward G., Boston, MA, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001011097	A1	20010802
APPLICATION INFO.:	US 2001-800855	A1	20010307 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-265299, filed on 9 Mar 1999, PENDING Continuation-in-part of Ser. No. US 1998-65012, filed on 23 Apr 1998, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-77977	19980313 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ARNALL GOLDEN & GREGORY, LLP, 2800 ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, ATLANTA, GA, 30309-3450
NUMBER OF CLAIMS: 34
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 526
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Methods and compositions for treating and preventing **mucositis**
AB A method of reducing or inhibiting **mucositis** in a patient, which includes administering an inflammatory cytokine inhibitor or a mast cell inhibitor, or a combination thereof, is. . .
SUMM [0002] This invention relates to methods and compositions for treating and preventing **mucositis**.
SUMM [0003] **Mucositis** is the destruction of the oral mucosal epithelium, which results in erythema, ulcerations and severe pain in the oral cavity. **Mucositis** often arises as a complication of antineoplastic therapy, such as cancer chemotherapy and/or radiation therapy. The painful ulcerative lesions of **mucositis** can cause patients to restrict their oral intake; as a result, they lose weight and suffer from fever associated with dehydration. Severe **mucositis** can necessitate the de-escalation of a planned

chemo/radio-therapeutic dosing regimen to prevent further damage to the oral mucosa.

SUMM [0004] An even more serious consequence of **mucositis** is that the lesions can act as sites of secondary infections and as portals of entry for endogenous oral microorganisms. **Mucositis** is therefore a significant risk factor for life-threatening systemic infection (septicemia); the risk of systemic infection is exacerbated by concomitant neutropenia, which is another complication associated with chemotherapy. Patients with **mucositis** and neutropenia have a relative risk of septicemia that is at least four times greater than that of individuals without **mucositis**.

SUMM [0005] The overall frequency of **mucositis** varies; it is influenced by the patient's diagnosis, age, and level of oral health, as well as the type, dose,. . . and frequency of drug or radiation administration. Approximately 40% of all patients who receive cancer chemotherapy suffer some degree of **mucositis**, and virtually 100% of patients treated with radiation therapy for head and neck tumors develop **mucositis**. The frequency of severe **mucositis** in patients undergoing high risk protocols is over 60%. About 50% of individuals develop lesions severe enough to require modification. . .

SUMM [0006] The development of effective methods for treating and preventing **mucositis** has been hampered by a lack of understanding of the pathophysiology of this condition, and by the inconsistency in patient. . .

SUMM [0007] The invention features methods for treating and preventing **mucositis**. The invention is based, in part, on the recognition that **mucositis** is a complex biological process resulting from the cumulative and interactive effects of radiation and/or chemotherapy with epithelial connective tissue. . .

SUMM [0008] We hypothesize that **mucositis** represents a clinical outcome due to a complex interaction of local tissue (connective tissue, endothelium, epithelium) toxicity, the level of. . .

SUMM . . . inflammatory cells expressing pro-inflammatory cytokines occurs during the breakdown of the mucosa and peaks just prior to the acme of **mucositis**. Bacterial colonization of the damaged epithelium occurs and is accelerated by the patient's myelosuppressed state. Typically the nadir follows a day or so after peak **mucositis**. Bacterial cell wall products from both gram positive and gram negative organisms likely then penetrate the injured mucosa and further. . .

SUMM [0010] According to the invention, **mucositis** can be treated, or even prevented, by the administration of inflammatory cytokine inhibitors, MMP inhibitors, and/or mast cell inhibitors. The. . . these inhibitors with an anti-inflammatory agent and/or an antimicrobial agent provides an even more effective regime for preventing and treating **mucositis**.

SUMM [0011] The invention features a method of reducing or inhibiting **mucositis**, in a patient suffering from **mucositis** or at risk for **mucositis**; the method includes administering to the patient a first therapeutic agent in an amount sufficient to inhibit **mucositis**, where the first therapeutic agent is an inflammatory cytokine inhibitor, a mast cell inhibitor, an MMP inhibitor, or a combination. . . mast cell inhibitors include degranulation inhibitors, antihistamines, and serine protease inhibitors. A preferred MMP inhibitor is a tetracycline such as **minocycline**, which used by itself in low doses is an effective **mucositis** agent that does not primarily act as an antibiotic. Other members of the tetracycline family can be used as well, e.g., chlortetracycline and oxytetracycline. An example of a **mucositis** that can be reduced

or inhibited according to the invention is oral **mucositis**.

SUMM [0012] The invention also features a method of treating, inhibiting, or preventing **mucositis** in the human patient by administering to the patient first and second different therapeutic agents, the first agent being an. . . an interferon-gamma inhibitor. A preferred combination is a TNF-alpha inhibitor combined with an MMP inhibitor such as a tetracycline, eg, **minocycline**. Exemplary NO inhibitors are aminoguanidine and guanidine. Another TNF-alpha inhibitor that can be used is thalidomide. Mast cell inhibitors can. . .

SUMM [0014] In another preferred method, the first therapeutic agent, in an amount sufficient to inhibit **mucositis**, and the third therapeutic agent, in an amount sufficient to inhibit infection, are administered. Preferably, the first therapeutic agent and. . .

SUMM [0015] The **mucositis** being treated can be induced by antineoplastic therapy; for example, it can be induced by chemotherapy or by radiation therapy.. . .

SUMM [0016] The invention further features a pharmaceutical composition for treating oral **mucositis** that includes (a) a first therapeutic agent including an inflammatory cytokine inhibitor, a mast cell inhibitor, an MMP inhibitor or. . . agent; and (c) a pharmaceutically acceptable carrier. The first and second therapeutic agents are present in amounts sufficient to inhibit **mucositis** in a patient suffering from **mucositis** or at risk for **mucositis**. Preferably, the composition is formulated into a lozenge, a tablet, an oral rinse, an oral paste, or an oral gel.. . . is an antihistamine; preferred anti-inflammatory agents include non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors. Preferred MMP inhibitors include tetracyclines such as **minocycline**, tetracycline HCl, or doxycycline. Preferred compositions can also include an anti-ulcer agent, in an amount sufficient to inhibit gastric mucosal. . .

DRWD [0017] FIG. 1 is a schematic representation illustrating the four phases of **mucositis** development and resolution.

DETD [0018] The invention features methods and compositions for reducing and inhibiting **mucositis** that include administering inflammatory cytokine inhibitors and/or mast cell inhibitors.

DETD [0019] The invention is based, in part, on the development of a new mechanistic scheme for the physiological basis of **mucositis**. According to this scheme, the development and resolution of **mucositis** occurs in four interrelated phases: (i) an inflammatory/vascular response; (ii) a degenerative connective tissue and/or epithelial phase; (iii) an ulcerative/bacteriological. . .

DETD . . . in the local levels of cytotoxic agents. Both IL-1 and TNF-.alpha. cause local tissue damage, and thereby initiate and accelerate **mucositis**.

DETD . . . also based, in part, on the discovery that proliferation of mast cells plays a key role in the development of **mucositis**. Mast cells are granule-containing secretory cells which are present in mucosal and connective tissues, and which can migrate within these. . .

DETD . . . the mast cells or the action of the mediators released by mast cells can be used to treat and prevent **mucositis**. Mast cell inhibitors are chemical or biological agents that suppress or inhibit the function of mast cells, or the mediators. . .

DETD [0034] According to the invention, inflammatory cytokine inhibitors can also be used to treat and prevent **mucositis**. Inflammatory cytokine inhibitors are chemical or biological agents that suppress or inhibit inflammatory cytokines. Such inhibitors include pyridinyl

imidazoles, bicyclic. . .

DETD [0035] Anti-inflammatory agents can be used in combination with inflammatory cytokine and/or mast cell inhibitors to treat and prevent **mucositis** according to the invention. Examples of anti-inflammatory agents that can be used in the present invention include the non-steroidal anti-inflammatory. . .

DETD . . . for the elevated production of prostaglandins during inflammation. COX-2 inhibitors are especially useful where the invention is used to treat **mucositis** in cancer patients undergoing chemotherapy or radiation therapy, because of the gastrointestinal tolerability of these inhibitors. COX-2 inhibitors that can. . .

DETD [0039] MMP inhibitors include both the antibacterial tetracyclines such as tetracycline HCl, **minocycline** and doxyocycline, as well as non-antibacterial tetracyclines.

DETD . . . agents in combination with the agents described above can result in an even more effective method for treating and preventing **mucositis**. Examples of antimicrobial agents that can be used include agents with spectrum for gram positive and gram negative organisms. Specific. . .

DETD [0041] Other agents that can be used to treat or prevent **mucositis** include the nuclear transcription factor kappa-B (NF-.kappa.B) activation inhibitors capsaicin and resiniferatoxin.

DETD [0044] Since the compositions of the invention can help prevent **mucositis**, administration of the compositions should preferably precede the initial dose of antineoplastic therapy by at least 24 hours. Daily treatment. . .

DETD [0059] For treatment according to the methods described herein, patients are dosed with a topical application of **mucositis** medication as a troche or lozenge, beginning the evening before the first dose of chemotherapy. The lozenge contains therapeutic doses of an MMP inhibitor such as **minocycline** and a nonsteroidal anti-inflammatory agent such as flurbiprofen.

DETD . . . assure exposure of the drug to the oropharynx. The fourteen-day dosing period provides coverage through the first three phases of **mucositis** development.

DETD . . . dose of radiation of about 60 Gy, given in divided doses over a 6-week to 8-week period. Early signs of **mucositis** are noted at doses of around 10 Gy, and frank breakdown of the mucosa is seen at around 25 Gy.

DETD [0063] Beginning with the second week of this type of radiation therapy, patients receive **mucositis** medication 2 hours prior to each daily dose of radiation, which is typically given 5 days per week. Subsequent **mucositis** medication is given 2 hours, 6 hours, and 12 hours following daily radiation. Since myelosuppression is not an issue for patients being radiated for head and neck cancers, the **mucositis** preparation includes mast cell inhibitors, cytokine inhibitors, and anti-inflammatory agents, but no anti-microbial agents. Patients do not receive **mucositis** medication on days on which they are not radiated. The protocol is followed until radiation dosing is completed.

DETD . . . specific anti-cancer drugs for treatment of this form of tumor, this group of patients is at particular risk for developing **mucositis**. Patients in this group begin dosing with **mucositis** medication two hours prior to chemotherapy administration. They continue taking **mucositis** medication every 4 hours, while awake, for at least the next 48 hours. The regimen is repeated for each dosing. . .

DETD . . . to treat and prevent conditions such as lichen planus and

graft-vs-host disease, which have similar biological mechanisms to that of **mucositis**.

CLM What is claimed is:

1. A method of treating, inhibiting, or preventing **mucositis** in a human patient, said method comprising administering to said patient first and second different therapeutic agents, wherein said first. . .

7. The method of claim 6 wherein said tetracycline is **minocycline**.

15. A method of treating, inhibiting, or preventing **mucositis** in a human patient, said method comprising administering to said patient an effective amount of a therapeutic agent selected from. . .

20. The method of claim 19, wherein the tetracycline is **minocycline**.

22. The method of claim 1, wherein said **mucositis** is induced by antineoplastic therapy.

23. The method of claim 22, wherein said **mucositis** is induced by chemotherapy.

24. The method of claim 22, wherein said **mucositis** is induced by radiation therapy.

27. The method of claim 1, wherein said **mucositis** is oral **mucositis**.

28. A pharmaceutical composition for treating oral **mucositis** comprising (a) a first therapeutic agent comprising an NSAID, an inflammatory cytokine inhibitor, or a mast cell inhibitor; (b) a. . . and (c) a pharmaceutically acceptable carrier, wherein said first and second therapeutic agents are present in amounts sufficient to inhibit **mucositis** in a patient suffering from **mucositis** or at risk for **mucositis**.

L14 ANSWER 4 OF 6 USPATFULL

AB The present invention is directed to methods of treating or protecting mucosal tissue from damage associated with radiation and/or chemotherapeutic treatment of cancers, by the topical application of amifostine and related compounds. These methods avoid the side effects of systemically applied radio/chemo protectants. The invention is also directed to treatment and prevention of infections associated with **mucositis** by topical application of amifostine and related compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2001:79144 USPATFULL
TITLE:	Topical administration of amifostine and related compounds
INVENTOR(S):	Stogniew, Martin, Blue Bell, PA, United States Bourhis, Jean, Sceaux, France
PATENT ASSIGNEE(S):	MedImmune Oncology, Inc., West Conshohocken, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6239119	B1	20010529

09/800,855

APPLICATION INFO.: US 1999-298824 19990426 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-83071	19980427 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Cintins, Marianne M.
ASSISTANT EXAMINER: Kim, Vickie
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 1096
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . side effects of systemically applied radio/chemo protectants. The invention is also directed to treatment and prevention of infections associated with **mucositis** by topical application of amifostine and related compounds.

SUMM . . . protection of mucosal tissue, and especially mucosal tissue of the head and neck regions, from chemical, radiation, and radio/chemo induced **mucositis** and conditions related to **mucositis** , associated with the treatment of cancers. The methods are achieved by the topical application of amifostine, structurally related compounds or their metabolites. The invention also encompasses treatment and prevention of infections associated with **mucositis** in mucosa of the head and neck region by topical application of amifostine and related compounds. Topical application of these. . .

SUMM . . . chemotherapy ("radio/chemo") protectant is especially acute in patients suffering from radiation or chemically induced damage to mucosal tissue, such as **mucositis** and conditions associated with **mucositis**. As a specific example, cancers of the head and neck are often highly localized, and would benefit from aggressive radio/chemo. . .

SUMM . . . Int. J. Radiat. Oncol. Biol. Phys., 32(3), 747-752 (1995). In all of the patients treated with the accelerated schedule, confluent **mucositis** was observed, and more than half of the patients required hospitalization to treat the **mucositis**. Similar results were reported by Delaney et al. (96% showed confluent **mucositis**), following a different aggressive radiotherapy schedule. Delaney et al., Int. J. Radiat. Oncol. Biol. Phys., 32(3), 763-768 (1995). But for. . .

SUMM . . . toxicity were reported. The study did not address protection of other tissues or of the oral mucosa per se from **mucositis**.

SUMM . . . small bowel. The study concluded that amifostine, and particularly amifostine in an alkaline vehicle, was an effective radioprotector against intestinal **mucositis** in rats.

SUMM . . . and neck region are particularly sensitive to radiation and chemically-induced damage association with radiochemical treatment of head and neck cancers. **Mucositis** of these tissues results in extreme patient discomfort, as well as in complications due to infection of ulcerated **mucositic** tissues. There has yet to be identified a safe and effective method of protecting the mucosal tissues of the head. . .

DETD . . . and/or after treatment with radiation or chemotherapeutics. This topical application can both treat and protect the patient from damage including **mucositis** and related disorders as well as bacterial infection.

DETD . . . is particularly well-suited to prevent or treat damage to the

mucosal tissues of the oral cavity to prevent or treat **mucositis** and related conditions and complications, including severe dry-mouth known as xerostomia. Thus, oral mucosal tissues are most preferred

DETD The term "protect" as used herein means to avoid, reduce the incidence of, or reduce the severity of **mucositis** and related conditions and complications and their symptoms.

DETD The term "treat" as used herein means to lessen or reverse the symptoms of **mucositis** and related conditions and complications.

DETD . . . retinoids, topical cardiovascular agents, clotrimazole, ketoconazole, miconozole, griseofulvin, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, monobenzone, erythromycin, tetracycline, clindamycin, meclocyline, hydroquinone, **minocycline**, naproxen, ibuprofen, theophylline, cromolyn, albuterol, retinoic acid, 13-cis retinoic acid, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, betamethasone valerate, betamethasone. . .

DETD The present invention also encompasses methods of preventing and treating infections, particularly those associated with **mucositis**, such as secondary infections that occur as a result of radiation and/or chemotherapy. Bacterial infection of mucosal tissues is a. . .

DETD The antibacterial properties can also be used advantageously to prevent and treat infections, particularly those associated with **mucositis**, when the amifostine compounds are applied topically. The antibacterial properties allow the topical use of the amifostine compound after irradiation or chemotherapy to protect against bacterial infection as well as symptoms of **mucositis**.

DETD Effect of Topical Administration of Amifostine on Radiation-induced **Mucositis** in Mice

DETD . . . and weighed each day. Any mice having lost 30% or more of the initial weight was sacrificed. The effect of **mucositis** and weight loss were compared at the maximum of the acute reactions (day 11) among the different groups receiving or. . .

DETD . . . and 400 mg/kg IP dosages, respectively. The error bars represent the standard error. For topical amifostine, the maximum grade of **mucositis** was found to be 3.9.+-.0.2, and was not statistically significantly different from the IP groups. The control group receiving no. . .

L14 ANSWER 5 OF 6 USPATFULL

AB Compositions and methods using the compositions for treatment of peripheral hyperalgesia are provided. The compositions contain an anti-hyperalgesia effective amount of one or more compounds that directly or indirectly interact with peripheral opiate receptors, but that do not, upon topical or local administration, elicit substantial central nervous system effects. The anti-diarrheal compound 4-(p-chlorophenyl)-4-hydroxy-N-N-dimethyl-.alpha.,.alpha.-diphenyl-1-piperidinebutyramide hydrochloride is preferred for use in the compositions and methods.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1999:155755 USPATFULL
TITLE:	Peripherally active anti-hyperalgesic opiates
INVENTOR(S):	Yaksh, Tony L., San Diego, CA, United States
PATENT ASSIGNEE(S):	Regents of the University of California, Oakland, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION:	US 5994372	19991130
APPLICATION INFO.:	US 1996-712881	19960912 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1995-528510, filed on 12 Sep 1995, now patented, Pat. No. US 5849761	
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Spivack, Phyllis G.	
LEGAL REPRESENTATIVE:	Seidman, Stephanie L.Heller Ehrman White & McAuliffe	
NUMBER OF CLAIMS:	29	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	9 Drawing Figure(s); 5 Drawing Page(s)	
LINE COUNT:	5274	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Tetracyclines such as Apicycline, Aztreonam, Chlortetracycline, Clomocycline, Colistimethate, Demeclocycline, Doxycycline, Elindamycin, lindamycin, Guamecycline, Linccomycin, Loracarbef, Lymecycline, Meclocycline, Methacycline, **Minocycline**, Novobiocin, Oxytetracycline, Penimepicycline, Pipacycline, Rolitetracycline, Sancycline, Senociclin and Tetracycline; and

DETD . . . example, poison ivy and diaper rashes, acne, insect bites/stings, skin ulcers, including, but not limited to, diabetic and decubitus ulcers, **mucositis**, inflammation, for example, periodontal inflammation, orthodontic inflammation, inflammatory conjunctivitis, hemorrhoids and venereal inflammations, gingivitis, bronchitis, laryngitis, sore throat, shingles, fungal. . . acne, insect bites/stings and skin ulcers (including diabetic and decubitus ulcers). Hyperalgesic conditions of the mouth, larynx and bronchium include **mucositis**, post-tooth extraction, periodontal inflammation, gingivitis, orthodontic inflammation, bronchitis, laryngitis and sore throat. Hyperalgesic conditions of the eyes include corneal abrasions,. . .

L14 ANSWER 6 OF 6 USPATFULL

AB In accordance with the present invention, there are provided conjugates of nitric oxide scavengers (e.g., dithiocarbamates, or "DC") and pharmacologically active agents (e.g., NSAIDs). Invention conjugates provide a new class of pharmacologically active agents (e.g., anti-inflammatory agents) which cause a much lower incidence of side-effects due to the protective effects imparted by modifying the pharmacologically active agents as described herein. In addition, invention conjugates are more effective than unmodified pharmacologically active agents because cells and tissues contacted by the pharmacologically active agent(s) are protected from the potentially damaging effects of nitric oxide overproduction induced thereby as a result of the co-production of nitric oxide scavenger (e.g., dithiocarbamate), in addition to free pharmacologically active agent, when invention conjugate is cleaved.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1999:72602 USPATFULL
TITLE:	Conjugates of dithiocarbamates with pharmacologically active agents and uses therefore
INVENTOR(S):	Lai, Ching-San, Encinitas, CA, United States
PATENT ASSIGNEE(S):	Medinox, Inc., San Diego, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE

09/800,855

PATENT INFORMATION:	US 5916910	19990629
APPLICATION INFO.:	US 1997-869158	19970604 (8)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Davis, Zinna Northington	
LEGAL REPRESENTATIVE:	Reiter, Esq., Stephen E.Gray, Cary, Ware & Freidenrich	
NUMBER OF CLAIMS:	27	
EXEMPLARY CLAIM:	1	
LINE COUNT:	1842	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . Gianni et al., in Rev. Biochem. Toxicol. 5:1-82 (1983)). In addition to cardiomyopathy, adriamycin administration causes cutaneous irritation and alopecia, **mucositis** (stomatitis and esophagitis), phlebosclerosis and hematologic toxicities and many other local and systemic toxicities.

SUMM . . . erythromycin ethylsuccinate, erythromycin, erythromycin estolate, erythromycin lactobionate, erythromycin siearate, erythromycin ethylsuccinate, and the like), tetracyclines (e.g., tetracycline hydrochloride, doxycycline hyclate, **minocycline** hydrochloride, and the like), and the like);

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L13 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

AB Pentoxifylline (PTX) has recently been shown to modulate TNF-.alpha. prodn. and to reduce the incidence and severity of all major complications after bone marrow transplantation (BMT), including **mucositis**, venoocclusive disease, renal insufficiency, hypertension, and graft-vs.-host disease. To analyze in detail the effect of PTX on immune complications after BMT, the authors investigated the immunomodulatory effect of PTX on immune responses in vitro. The continuous presence of PTX significantly reduced the proliferative response of PBMC to PHA stimulation and to alloantigens in a dose-dependent manner. Starting at concns. of 100 .mu.g/mL, PTX was able to inhibit and, at 1000 .mu.g/mL, completely block mitogen-induced proliferation. Maximal inhibition of more than 90% (91 .+-. 4%) was also obsd. at PTX concns. of 1000 .mu.g/mL in the mixed lymphocyte culture (MLR) and by addn. on day 0. However, lower but still significant suppression (13 .+-. 7%) was achieved at concns. of 10 .mu.g/mL PTX. The inhibitory capacity of PTX was increased by mAbs against TNF-.alpha. (34 .+-. 5% addnl. suppression at 100 .mu.g/mL PTX) and not reversed by the addn. of rTNF-.alpha.. The effect of PTX on the generation of CTLs in vitro was studied in the cell-mediated lymphotoxicity assay. PTX (100 .mu.g/mL) significantly inhibited (P = 0.0178) the in vitro generation of CTLs when PTX was added to the culture on day 0. PTX also showed profound modulatory properties in the NK assay, with a redn. of 23 .+-. 3% in specific lysis at 10 .mu.g/mL PTX and maximal redns. of 88 .+-. 3% at 1000 .mu.g/mL PTX. Immunomodulatory properties of PTX were not only assocd. with blockage of TNF-.alpha., as shown by decreased mRNA expression and TNF-.alpha. values in the culture supernatants, but also with an impaired prodn. of other cytokines and secondary messages such as IFN-.gamma. and neopterin. PTX treatment, however, did not affect IFN-.alpha. or IL-1.beta. prodn., and IL-6 release was even increased. PTX, therefore, has profound immunomodulatory properties in vitro, which are assocd. with selective inhibition of cytokine release and can be enhanced by the addn. of mAbs against TNF-.alpha., but not reversed by the addn. of rTNF-.alpha..

ACCESSION NUMBER: 1994:124446 CAPLUS
DOCUMENT NUMBER: 120:124446
TITLE: Immune response modulation by pentoxifylline in vitro
AUTHOR(S): **Tilg, Herbert**; Eibl, Brigitte; Pichl, Marion; Gaechter, Anne; Herold, Manfred; Brankova, Juliana; Huber, Christoph; Niederwieser, Dietger
CORPORATE SOURCE: Dep. Intern. Med., Univ. Hosp., Innsbruck, 6020, Austria
SOURCE: Transplantation (1993), 56(1), 196-201
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English

AU **Tilg, Herbert**; Eibl, Brigitte; Pichl, Marion; Gaechter, Anne; Herold, Manfred; Brankova, Juliana; Huber, Christoph; Niederwieser, Dietger

AB Pentoxifylline (PTX) has recently been shown to modulate TNF-.alpha. prodn. and to reduce the incidence and severity of all major complications after bone marrow transplantation (BMT), including **mucositis**, venoocclusive disease, renal insufficiency, hypertension, and graft-vs.-host disease. To analyze in detail the effect of PTX on immune complications after BMT, the authors investigated the immunomodulatory effect of PTX on immune responses in vitro. The continuous presence of

PTX significantly reduced the proliferative response of PBMC to PHA stimulation and to alloantigens in a dose-dependent manner. Starting at concns. of 100 .mu.g/mL, PTX was able to inhibit and, at 1000 .mu.g/mL, completely block mitogen-induced proliferation. Maximal inhibition of more than 90% (91 .+-. 4%) was also obsd. at PTX concns. of 1000 .mu.g/mL in the mixed lymphocyte culture (MLR) and by addn. on day 0. However, lower but still significant suppression (13 .+-. 7%) was achieved at concns. of 10 .mu.g/mL PTX. The inhibitory capacity of PTX was increased by mAbs against TNF-.alpha. (34 .+-. 5% addnl. suppression at 100 .mu.g/mL PTX) and not reversed by the addn. of rTNF-.alpha.. The effect of PTX on the generation of CTLs in vitro was studied in the cell-mediated lymphotoxicity assay. PTX (100 .mu.g/mL) significantly inhibited (P = 0.0178) the in vitro generation of CTLs when PTX was added to the culture on day 0. PTX also showed profound modulatory properties in the NK assay, with a redn. of 23 .+-. 3% in specific lysis at 10 .mu.g/mL PTX and maximal redns. of 88 .+-. 3% at 1000 .mu.g/mL PTX. Immunomodulatory properties of PTX were not only assocd. with blockage of TNF-.alpha., as shown by decreased mRNA expression and TNF-.alpha. values in the culture supernatants, but also with an impaired prodn. of other cytokines and secondary messages such as IFN-.gamma. and neopterin. PTX treatment, however, did not affect IFN-.alpha. or IL-1.beta. prodn., and IL-6 release was even increased. PTX, therefore, has profound immunomodulatory properties in vitro, which are assocd. with selective inhibition of cytokine release and can be enhanced by the addn. of mAbs against TNF-.alpha., but not reversed by the addn. of rTNF-.alpha..

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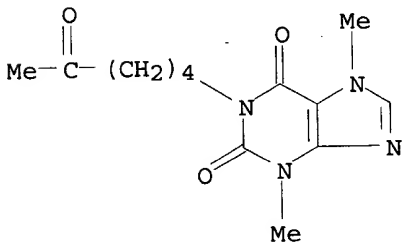
=> s e3
L1 1 PENTOXIFYLLINE/CN

=> d l1

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 6493-05-6 REGISTRY
CN 1H-Purine-2,6-dione, 3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Theobromine, 1-(5-oxohexyl)- (7CI, 8CI)
OTHER NAMES:
CN 1-(5-Oxohexyl)-3,7-dimethylxanthine
CN 1-(5-Oxohexyl)theobromine
CN 3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione
CN 3,7-Dimethyl-1-(5-oxohexyl)-1H,3H-purin-2,6-dione
CN 3,7-Dimethyl-1-(5-oxohexyl)xanthine
CN Agapurin Retard
CN BL 191
CN Dimethyloxohexylxanthine
CN Oxpentifylline
CN Pentoxifyllin
CN **Pentoxifylline**
CN Pentoxiphyllin
CN Pentoxiphylline
CN Pentoxyfilline
CN Pentoxyphyllin
CN PTX
CN Torental
CN Trental
FS 3D CONCORD
MF C13 H18 N4 O3
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, TOXLIT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

Delacroix

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1741 REFERENCES IN FILE CA (1967 TO DATE)
20 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1746 REFERENCES IN FILE CAPLUS (1967 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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